The role of (shared) genetics and environment in (co-occurring) psychiatric problems, substance use, and obesity

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General discussion
Chapter 7

General discussion

In this thesis, I investigated the influence of (shared) genetic and environmental factors on psychiatric problems, substance use, obesity, and their co-occurrence. In this final chapter, I will first summarize the main findings of my thesis. Next, I will put these into perspective by linking them to results of recent studies in the field, provide emerging themes in relation to the study design and methodology that I used in my chapters and discuss future research directions.

Summary of main findings

Part 1: Familial (co)aggregation

In Chapter 2, we investigated the familial (co)aggregation and (shared) heritability of depression, anxiety, obesity, and substance use in the multi-generational population-based Lifelines Cohort Study (n=162,423). The study found that depression, anxiety, obesity, and substance use aggregated within families as well as between spouses. All phenotypes were moderately heritable. In addition, depression, anxiety, obesity, and smoking showed positive familial co-aggregation, where each conferred increased risk on all the other conditions within families, consistent with the positive genetic correlations (rG) between these outcomes. This study provided insights into the patterns of genetic overlap between depression, anxiety, obesity, and substance use, which may aid to uncover the mechanisms underlying familial co-aggregation.

In Chapter 3, we estimated the familial (co)aggregation and (shared) heritability of attention-deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) with each other and with aggressive behavior, depression, anxiety, and substance use in a subset of the Lifelines Cohort Study (n=37,716). The study found that neurodevelopmental problems recurred within families and were moderately heritable. Specifically, we estimated heritabilities of and genetic correlations between two subdomains of ADHD and six subdomains of ASD. The findings indicated a high level of homogeneity within both the ADHD and ASD subdomains, with stronger similarities observed among subdomains belonging to the same disorder compared to cross-disorder subdomains. Furthermore, all neurodevelopmental problems had both strong phenotypic and genetic links with aggressive behavior, while the links of ADHD and ASD with depression and anxiety mainly existed at the genetic level, and the links with substance use were relatively weak. The identified genetic overlap in this study suggests shared etiological mechanisms, and a more detailed examination of the heterogeneity within ADHD and ASD subdomains provided new insights that could guide future research.
Part 2: Molecular gene-environment interaction (G×E) studies

In Chapter 4, we examined moderation effects of stress-related exposures on polygenic risk scores (PRSs) for depression and anxiety using genome-wide data in the Lifelines Cohort Study (n=41,810). The study found that reduced social support, and higher exposure to long-term difficulties, stressful life events, and loneliness amplified the genetic effects on both depression and anxiety. For childhood trauma exposure, the interaction with the PRS was significant for depression but not for anxiety. This study provided evidence on the presence of polygenic risk-by-stress interaction in relation to depression and anxiety.

In Chapter 5, we examined moderation effects of socio-economic status (SES) on PRSs for depression, anxiety, substance use and obesity, and applied genomic structural equation modelling (genomic SEM) to investigate these moderation effects at higher aggregated genetic levels for aggregated phenotypic outcomes (i.e., depression/anxiety, BMI/waist-hip-ratio (WHR), and smoking/alcohol use and a common factor across these three domains) using the genome-wide genotyped data in the Lifelines Cohort Study (n=50,761). The study found that lower SES amplified the effect of PRSs on depression, anxiety, body mass index (BMI), and smoking, while higher disposable income amplified the effect of PRS on alcohol use. For aggregated outcomes, nine of sixteen investigated interactions between four SES indices (educational attainment, occupational status, household disposable income, and neighborhood SES) and four shared PRSs were significant for the latent depression/anxiety, BMI/WHR, and smoking/alcohol use domains as well as the common factor across the three domains. This study provided evidence on the presence of polygenic risk-by-SES interactions at the level of individual PRS and depression, anxiety, BMI, and substance use. However, effect sizes of interactions were attenuated between the shared genetics and SES for aggregated outcomes. Thus, the genomic SEM approach that was taken in this study on moderation effects of SES on PRSs gave no additional etiological understanding of the co-occurrence of studied phenotypes.

Part 3: PRS and family history as predictors of obesity

In Chapter 6, we investigated the influences of PRS and family history on indices of general and abdominal obesity using between and within family approaches in the Lifelines Cohort Study (n=50,747). In addition to genetic parent-offspring transmission captured by the PRS, family history indexed by parental BMI, waist circumference (WC) and WHR additionally predicted offspring’s BMI, WC and WHR. The latter may reflect additional genetic effects not captured by PRS as well as effects of the family environment. Similar effects of between- and within-family PRS among siblings indicated that there was little bias in the genetic effects on indices of obesity due to so called genetic nurture (i.e., gene-environment correlations). This study showed that
the combination of PRS and family history improved the prediction of BMI, WC and WHR and confirms that bias induced by gene-environment correlation on effects of genome-wide estimates for obesity susceptibility (i.e., PRSs) is limited.

Discussion of the main findings

Family studies and molecular genetic designs

In the pre-genome-wide association study (GWAS) era, twin or family studies were used to investigate genetic effects on diseases. In Chapters 2 and 3, we estimated the heritabilities of psychiatric problems, substance use and obesity, which were similar to estimates in previous family studies\(^2\), but lower than those estimated in twin studies\(^3\,\,\,^5\). We found heritability estimates of 0.25 for depression, 0.26 for anxiety, 0.33 for ADHD, 0.39 for ASD, and 0.53 for BMI, while in twin studies heritability estimates were 0.37 for depression\(^7\), 0.32 for generalized anxiety disorder (GAD)\(^4\), 0.76 for ADHD\(^5\), 0.80 for ASD\(^6\), and 0.75 for BMI\(^2\). These differences in the heritabilities between family and twin studies varied for the different phenotypes, and were typically largest for childhood onset disorders including ADHD and ASD. The most likely explanation of the consistently lower heritabilities estimated in family studies is that partly different genes may influence the phenotype of interest at different ages\(^7\). The age difference in family studies may reduce the correlations (and thereby the heritability estimates) between relatives compared to same aged twins\(^8\). For childhood onset disorders like ADHD and ASD, an additional source of age-related reductions in heritability in family studies is that in childhood these phenotypes are measured based on parent ratings while in adulthood these are based on self-report. Typically, parent and self-ratings show only moderate levels of agreement and thus this informant-change likely adds to reduced correlations between family members\(^8\). To investigate the presence of age-dependent effects, researchers have conducted studies examining parent-offspring relationships, where both parents and offspring were assessed at the same age. An example of supporting evidence that age differences reduce heritability estimates comes from a study\(^10\) involving a sample of 1,141 parent pairs aged 48-51, who had their blood pressure measured. Subsequently, two to three decades later, blood pressure measurements were obtained from 2,497 of their offspring. The parent-offspring correlations for systolic blood pressure (SBP) ranged from 0.13 to 0.25 and for diastolic blood pressure (DBP) they ranged from 0.17 to 0.22. These values were found to be similar to the sibling-pair correlations of similar age for SBP (0.17-0.23) and DBP (0.19-0.24). In general, both family studies and twin studies have advantages. Twin studies provide an opportunity to estimate heritability and disentangle the contributions of shared genes and shared environment among twin pairs\(^11\). On the other hand, family studies involve a broader range of relatives, leading to larger samples, and findings can be generalized to the wider population.
In the GWAS era, a large number of genetic variants associated with traits and diseases have been identified. Another advantage is that this design allows estimation of the SNP-based heritability ($h^2_{SNP}$), which is the proportion of variance in genetic liability explained by common SNPs based on GWAS data. However, the $h^2_{SNP}$ generally only explains a small part of the total heritability estimated from twin or family studies. This gap is known as “missing heritability.” In Chapters 2 and 3, the difference between $h^2_{SNP}$ and the heritability estimated in our family study was 0.11 for ADHD, 0.14 for depression, and 0.25 for BMI. Furthermore, in Chapters 4 and 5, PRSs explained 0.66% of the variance in depression, 0.69% in anxiety, 1.04% in alcohol use, 2.36% in smoking, and 8.63% in BMI. These estimates are, in turn, much smaller than the $h^2_{SNP}$ (i.e., 11% for depression, 26% for anxiety, 4.2% for alcohol use, 7.8% for smoking, and 28% for BMI). The large gap between the variance explained by PRSs and $h^2_{SNP}$ is denoted as hidden heritability. The gap can be narrowed if more common genetic variants are identified with increased sample size as well as advanced PRS calculation methods, such as MegaPRS and SBayesRC. However, even for body height for which all genetic effects of common variants have been identified (also referred to as a saturated map of common genetic variants), the $h^2_{SNP}$ still only explains 40-50% of phenotypic variation, while the total heritability is estimated as 80% in the general population. Thus, still 30-40% of the heritability cannot be explained in this prototypic complex phenotype. Thus, the gap between SNP-based heritability and total heritability is thought to be mainly caused by rare and structural variants (e.g., duplications, inversions, and translocations) that cannot be measured or tagged by SNPs on the GWAS array. A recent study on height and BMI using whole genome sequence (WGS) data identified that rare variants, in particular those in regions of low linkage disequilibrium, are a major source of the still missing heritability (i.e., the difference between common SNP heritability and total heritability). SNP-based heritability based on common genetic variants was 0.48 for height and 0.24 for BMI, while the heritability based on WGS data with minor allele frequency (MAF) > 0.0001 increased to 0.70 for height and 0.29 for BMI, but the difference between total and common SNP heritability implying contribution of rare variants may differ for different phenotypes. Future research based on whole genome sequencing will enable the discovery of rare variants related to traits and diseases, which will reduce the still-missing heritability.

**Shared genetics**

Psychiatric problems and chronic diseases often co-occur within families. In Chapters 2 and 3, we estimated familial co-aggregation across psychiatric problems, substance use, and obesity at the phenotypic level. The recurrence risk ratio across the different phenotypes ranged from 0.86 for obesity in individuals with a positive family history of drug use to 2.56 for aggressive behavior in individuals with a positive family history of ADHD. The genetic correlations ranged from -0.14 between alcohol use and BMI...
to 0.94 between depression and anxiety. The estimates in the two family studies in
my thesis are comparable with those in the molecular studies (e.g., rGs of -0.15 to
-0.09 between alcohol consumption and BMI23, 24, 0.52-0.56 between major depressive
disorder and ADHD25, 26, and 0.79-0.82 between depression and anxiety25). The genetic
correlations measured in the current study quantify the genetic overlap between two
traits, which may indicate pleiotropic effects of genes27. However, whether shared genes
simultaneously influence biological pathways of two traits (horizontal pleiotropy) or one
trait has causal effects on the other trait (vertical pleiotropy)27 is still mostly unknown.
A relatively recent approach known as the latent causal variable (LCV) method has
been developed to explore the causal relationship between two genetically correlated
traits28. This method involves the use of a latent variable that mediates the genetic
correlation between two traits and has a causal effect on each trait. The LCV method
is based on the principle that if trait 1 is causal for trait 2 but trait 2 not for trait 1,
SNPs affecting trait 1 will have effects on trait 2, but not vice versa. Thus, if trait 1
is perfectly genetically correlated (i.e., rG = 1) with the latent factor, trait 1 is fully
genetically causal for trait 2. In practice, we generally do not find genetic correlations
of 1. The reasoning is then: if the latent variable exhibits a stronger genetic correlation
with trait 1 compared to trait 2, trait 1 is assumed to be partially genetically causal for
trait 2. This proportion of the genetic component of trait 1 that is causally related to
trait 2 can be quantified using the genetic causality proportion (GCP). For example,
one study showed that the genetic correlation between depression and obesity was
estimated as 0.32, where LCV indicated with a GCP of -0.70 that 70% of the genetic
correlation was due to a causal effect of obesity on depression29. Provided that the
assumptions are reasonable, this method would allow us to further explore the direction
of potential causality of genetic correlations in future research. Another way forward
is Local Analysis of Variant Association (LAVA)30. Genetic correlations typically reflect
the genome-wide average of the shared genetics, which might be underestimated
because of the mixture of concordant and discordant genetic associations between
the two phenotypes across the genome. LAVA was developed to estimate local genetic
correlations within specific genetic regions. Linked to this, a bivariate causal mixture
model (MiXeR)31 was developed to estimate the proportion of shared “causal” variants
with concordant effects, where common genetic variants can be divided into shared
“causal” variants, unique “causal” variants for each trait, and noncausal variants. In the
paper that developed and applied MiXeR, for instance, ADHD has 5.6K “causal” variants.
Depression was more polygenic with 14.5K “causal” variants31. Among these “causal”
variants, 4.4K variants were shared between ADHD and depression. The findings
indicated further that underlying the overall moderate genome-wide genetic correlation
(rG = 0.45), there were strongly correlated shared “causal” variants between ADHD and
depression (e.g., rG = 0.93), indicating that shared variants have similar effects for both
disorders, providing further insight into the mechanisms underlying the comorbidity
between ADHD and depression31.
An advanced approach to studying the joint genetic architecture of correlated diseases is genomic structural equation modeling (GSEM). In this method, multivariate GWASs are conducted to investigate the shared genetic liabilities across diseases, which are captured as latent broad genetic risk factors. In Chapter 5, we applied genomic SEM to estimate the shared genetic liabilities between depression, anxiety, obesity, and substance use. The shared PRS explained 5.36% for the aggregated outcome of BMI and WHR, which was the average of the variance explained for individual phenotypes (8.63% for BMI and 2.19% for WHR). Furthermore, for depression and anxiety, the shared PRS explained less variance for the aggregated outcome of depression and anxiety (0.62%) than for individual phenotypes (0.80% for depression and 0.74% for anxiety). One possible explanation of the reduced explanatory value of shared PRSs is that with more multivariate GWASs included in the GSEM model, there are fewer variants shared across multiple diseases reducing explained variance. Another potential reason is that the shared genetic variants may have concordant and discordant effects across diseases, and the heterogeneity across genetic variants may underestimate the shared genetic effects. In this thesis, our findings show smaller effects for GSEM derived PRSs and aggregated outcomes compared with individual outcomes, suggesting that genetic aggregation across diseases does not currently appear to enhance our understanding of shared etiological factors. However, we believe that future studies can benefit from the development of advanced approaches such as LCV, LAVA, MiXeR, and GSEM. To further our understanding of complex diseases and their aggregation, future studies should focus on identifying causal relationships between traits. Additionally, distinguishing shared genetic variants with concordant and discordant effects across diseases, both at the genome-wide level and within local genetic regions, is essential to uncover the underlying etiology of aggregation of complex diseases.

GxE interactions

In addition to the genetic risks, environmental factors, such as stress exposures and socio-economic status, have emerged as important determinants of psychiatric problems, obesity, and substance use. Specifically, individuals who experience long-term difficulties, stressful life events, childhood trauma, loneliness, and reduced social support are at a higher risk for developing depression and anxiety, consistent with previous research. Notably, stress exposures were found to explain larger proportions of variance in depression and anxiety than PRSs, which explained 0.66% for depression and 0.69% for anxiety, ranging from 3.30% for social support in depression to 16.60% for long-term difficulties in anxiety. Furthermore, lower levels of educational attainment, occupational status, household disposable income and neighborhood socio-economic status (NSES) are associated with an increased risk of depression, anxiety, obesity, and smoking, which aligns with previous findings that people from a lower SES background are more vulnerable to poor mental and physical health. The proportion of variance explained by SES was found to be smaller than stress exposures, ranging
from 0.01% for NSES in alcohol use to 1.68% for educational attainment in smoking. However, environmental exposures may have a heritable component as confirmed by recent studies with estimates of SNP-based heritability of 0.05 for stress-sensitivity\textsuperscript{46} and 0.12 for educational attainment\textsuperscript{47}. Additionally, another study indicated that SES is genetically correlated with psychiatric disorders and substance use (rG for SES was -0.66 with ADHD, -0.52 with depression/anxiety, -0.50 with smoking initiation, and -0.25 with alcohol use quantity)\textsuperscript{48}. The same study further showed that the SNP-based heritabilities of psychiatric disorders were attenuated after removing genetic SES variance, with the greatest reduction observed for ADHD from 0.25 to 0.14\textsuperscript{48}. Similar attenuation was also observed for gene-environment interactions. Specifically, the interaction between PRS and neighborhood income for lifetime smoking became non-significant when SNP-based genetic educational attainment variance was removed\textsuperscript{49}.

In the current thesis, significant interactions were observed between educational attainment and occupational status and PRS for smoking. However, it is unclear whether these interactions would remain significant if the genetic variance of environmental exposures would be removed. To address this question, future studies could apply genomic SEM to remove the genetic variance of environmental exposures from the PRS for the traits of interest. This approach would enable us to estimate the interactions between environmental exposures and PRS while controlling for the genetic influence on environmental exposures. While this may give additional insights into the extent of truly environmental and genetic risks and their interactions, the necessity of removing the genetic component of these environmental exposures is still a subject of debate, as environmental exposures such as stress exposures or SES have a heritable component.

The influence of an individual’s genetic make-up on the environment they experience, known as gene-environment correlation (rGE)\textsuperscript{50}, may confound gene-environment interactions (G×E)\textsuperscript{51}. Recent findings by Akimova et al suggest that higher rGE values could lead to an underestimation of the genetic main effect (i.e., from PRS), but very little inflation in the G×E effect\textsuperscript{52}. In addition, only small rGEs were found in current thesis. However, further simulation analyses indicated that the presence of unobserved confounders and their interactions with environmental exposures may inflate the G×E effect\textsuperscript{52}. In Chapter 4, we adjusted for four measures of SES as potential confounders, after which the interaction effects between stress exposures and PRSs only slightly attenuated while remaining significant, indicating the consistency of the interactions between PRSs and stress exposures for depression and anxiety. In the current thesis, we only considered SES as potential confounder. Thus, we most likely only partly addressed the potential effects of rGEs on G×E estimates. Recent studies propose that the use of a family design can quantify the rGE effects (also known as genetic nurture)\textsuperscript{1}. For instance, the impact of parental rearing environment on offspring health can be evaluated through associations between educational attainment polygenic scores constructed from non-transmitted parental alleles and offspring health outcomes\textsuperscript{1}. Furthermore,
and explained in the next section, the distinction between within- and between-family PRS effects among siblings could also quantify rGE effects$^{53}$.

**Using family designs in molecular genetic studies**

The findings of GWAS studies based on unrelated individuals not only capture pure genetic effects but may also be biased by other effects such as gene-environment correlations, population stratification and assortative mating, which may result in an inflation of GWAS effect estimates$^{54}$. Family-based GWAS designs can help mitigate this bias by comparing members of the same family (e.g., siblings)$^{55}$, leveraging the fact that siblings share the same parents, population stratum and family environment. In the current thesis, we found similar effect sizes of between- and within-family PRS for indices of obesity, indicating little bias in the genetic estimates. Consistent with our findings, a recent within-family GWAS demonstrated that within-sibship SNP-based heritability for BMI (within-sibship $h^2$ of 0.20) was similar to the population estimate (population $h^2$ of 0.27)$^{54}$. However, inflations of GWAS effects may vary for different traits. For instance, a recent within-family GWAS showed a strong reduction in SNP-based heritability estimates for educational attainment (~76% reduction), cognitive ability (44% reduction), ever smoking (25% reduction), and height (17% reduction)$^{54}$. In line with these findings, between-family PRS show stronger associations than within-family PRS with cognitive variables, including educational attainment and intelligence, but not for non-cognitive traits such as BMI and body height$^{53}$. Adjusting for family SES attenuates the difference between within- and between-family PRS for cognitive variables, indicating that SES is a major source of the between-family component, probably acting through rGE mechanisms$^{53}$. Population stratification, due to variations in allele frequencies among different ancestries, also introduces bias in the associations between genotype and phenotype. While methods such as adjusting for principal components of genetic variation in the study population and linear mixed models control for ancestry, they may not fully account for fine-scale population structure (i.e., subtle or localized genetic variations within the population). The within-sibship effect in GWAS is not influenced by population stratification$^{54}$. Finally, assortative mating, where individuals select a partner based on phenotypic similarity, may lead to positive correlations between two independent genetic variants associated with a phenotype in each parent. Additionally, this phenomenon may induce correlations between the genetic factors contributing to the phenotype in subsequent generations$^{54}$. Any bias caused by assortative mating is controlled in within-sibship estimates of genetic effects. The findings discussed above highlight the importance of considering potential bias in GWAS studies and the benefits of family-based designs for mitigating these biases due to gene-environment correlations, population stratification and assortative mating.
Chapter 7

Future perspectives

In recent decades, the GWAS field has witnessed rapid growth and numerous SNPs have been identified for complex diseases. To identify more genetic risk variants related to psychiatric disorders, researchers have employed a strategy of using broad disease definitions to increase the sample size, such as with broad depression. However, this approach may result in the identification of genetic variants for more general characteristics of depression that may only partially overlap with specific genetic variants related to depression. As sample sizes will become larger, future studies will be able to conduct GWASs focused on severe MDD and MDD subtypes and identify the more specific genetic variants. Furthermore, it is important to pinpoint the causal genes and variants, and examine whether the target genes are expressed in specific cells and tissues or enriched in particular networks and pathways. This would be beneficial for identifying potential drug targets and advancing treatments for psychiatric disorders.

Another promising avenue for future research involves conducting GWASs encompassing multi-ancestral populations. The prevailing trend in 2021 revealed that approximately 86% of GWAS participants were of European ancestry. The transferability of findings from GWAS conducted in European ancestry to other ancestries is limited, due to the differences in haplotype frequencies as well as variations in environmental and cultural aspects (e.g., diet habit) across diverse populations. As an illustration, the genetic correlation between East-Asian and European ancestry populations was 0.4 for major depression. Furthermore, it was observed that BMI has a positive genetic correlation with major depression in Europeans, but a negative genetic correlation among East-Asian populations. This makes clear that future investigations need to place greater emphasis on the inclusion of diverse populations in genetic research.

The predictive value of PRS for complex diseases may be applied into clinical settings. The present thesis showed that the predictive utility of PRS varied across different phenotypes, as it accounts for 8.63% of variance in BMI but less than 1% in depression and anxiety. Thus, PRSs for depression and anxiety need to improve before being clinically useful, for example based on larger GWASs or more powerful PRS calculation methods. Recent studies applied the multi-polygenic score (MPS) approach to increase predictive power by exploiting the joint power of multiple GWASs. They found that MPSs can account for more variance in certain traits, such as educational attainment, cognitive ability, and BMI, compared to the best single score predictions. Additionally, even GWASs of genetically distant traits might contribute predictive power if they have a much greater sample size, as seen with the predictive effect of educational attainment for cognitive ability. Given the moderate to high genetic correlations among psychiatric disorders, it may be beneficial for future studies to explore the potential of combining multiple PRSs for various psychiatric disorders to predict specific psychiatric outcomes, although this may lead to some loss in specificity. Additionally, the use of
PRS for cardiometabolic diseases, such as coronary artery disease (CAD), supported the usefulness of incorporating PRS into clinical risk tools to improve the accuracy of classification of CAD: 10.4% of incident CAD cases were misclassified as low risk by a clinical risk tool, which reduced to 4.4% misclassification by integrating PRS into the clinical risk tool\textsuperscript{62,63}. Moreover, incorporating family history along with PRS can further enhance predictive effects\textsuperscript{64}. For instance, PRS and family history individually explained 0.86% and 5.5% of the variance in depression, respectively, and their combination accounted for 6.1% of the variance in depression\textsuperscript{64}. Similarly, the present thesis reveals enhanced prediction for obesity through the combination of PRS and family history. Thus, future studies may consider incorporating MPSs, family history and clinical risk factors to develop more precise prediction models for classifying the incidence or presence of complex diseases.

The translation of genetic research findings into clinical personalized medicine is a crucial next step. The Estonian Biobank offers a good example, where personalized genome-based medicine is incorporated into national personalized medicine clinical pilots. The objective is to provide participants with a clear and comprehensive report that includes details about how the risk of disease will increase with age, the genetic contribution to the risk, and the extent to which it can be altered by lifestyle or medical interventions\textsuperscript{65}. Moreover, proper medical support such as genetic counseling, easy access to medical professionals and follow-up will be provided\textsuperscript{65}. Indeed, a recent study has highlighted that the translation of PRSs from discovery to clinical application requires at least three essential phases\textsuperscript{66}. The first phase involves epidemiology and statistical genetics, wherein PRSs are developed and validated in large population studies, similar to the work in the current thesis. The second phase involves the laboratory, wherein laboratory geneticists establish a pipeline that is analytically and clinically valid to compute, interpret, and report PRS results for individual patients. The third phase relates to patient care, where treating physicians make medical decisions by contextually analyzing patients’ PRS results. To develop the workflow of phases 2 and 3, the clinical trial “Genomic Medicine at Veterans Affairs (GenoVA) study” was conducted\textsuperscript{66}. The study generated clinical PRS laboratory reports for patients and their primary care physicians on five diseases, including coronary artery disease, type 2 diabetes mellitus, atrial fibrillation, colorectal cancer, and either prostate cancer in male patients or breast cancer in female patients. The study applied a cut-off odds ratio of 2 to identify individuals with a high genetic risk of developing certain diseases. After confirming the robustness of the developed pipeline as a clinical PRS assay in >35,000 biobank participants, it was applied to 227 individuals from the GenoVA study. The frequency of PRSs with an odds ratio > 2 ranged from 5.7% for colorectal cancer to 15.3% for prostate cancer. During the ongoing observation period in the GenoVA study, further clinical management steps could be taken based on PRSs results, allowing primary care physicians to provide personalized patient care. However, it is important to note that PRS is primarily used for disease prediction and not for diagnostic purposes. The
overall hope is that by providing genetic evidence pertaining to complex diseases, PRS may aid clinicians in early disease detection, facilitating the application of personalized medicine. The aforementioned examples show that there is still a long way to go before PRS information will be broadly integrated in clinical applications. This is especially true for predicting the future onset of psychiatric disorders.
Conclusions

The present thesis offers insights into the familial co-aggregation and shared genetics between psychiatric problems, obesity, and substance use based on a large family study. Further research utilizing advanced genetic methods is necessary to better understand the mechanisms driving these shared genetics. The thesis also provides evidence for the presence of polygenic risk-by-stress interaction effects in relation to depression and anxiety, as well as polygenic risk-by-SES interaction in relation to depression, anxiety, obesity, and substance use. These were proof of principle studies, where again we do not know the exact mechanisms yet. In the latter risk-by-SES study, interaction effects were relatively smaller at the aggregated phenotypic level. This suggests that modelling the genetic and phenotypic overlap of (aggregated) disease outcomes yielded no additional etiological understanding. Finally, the thesis demonstrated that combining family history and PRS led to improved prediction for indices of obesity. In this study, we used the family design to explore the parental-offspring transmission, as well as the within- and between-family PRS effects among siblings, revealing little bias in the genetic estimates for indices of obesity. Similar studies may clarify if this conclusion extends to other phenotypes, like depression, anxiety, and substance use.
References


