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

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General introduction
Chapter 1

Introduction

Psychiatric problems, substance use and obesity often co-occur\(^1\), which is not fully understood. Such problems not only co-occur within the same person but also co-aggregate within families. Familial aggregation is partly explained by genetic risk\(^2\)-\(^6\). In addition, environmental factors, such as stress exposure or low socio-economic status (SES), are risk factors for the co-occurrence\(^7\)-\(^11\). However, few studies so far have focused on whether and to what extent environmental factors moderate genome-wide association studies (GWAS)-based measures of genetic risk on these problems\(^10\)-\(^14\). Additionally, whether such interplay would be more potent when focused on the shared genetic susceptibility for their co-occurrence is unknown. Therefore, this thesis aims to improve our understanding of the effects of shared genetics and environment on psychiatric problems, substance use, obesity, and their co-occurrence. In this first chapter, I discuss the background and core concepts, identify knowledge gaps, describe aims and provide an outline of this thesis.

Phenotypes, prevalence, and co-occurrence

There are many types of psychiatric problems. Major depression (MDD), and anxiety disorders (ANX) comprise the most common group of psychiatric disorders, with a lifetime prevalence of 15.0-18.0% for depression\(^15\) and up to 33.7% for all anxiety disorders\(^16\). Attention-deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) are neurodevelopmental disorders, with a prevalence of 5.0-7.0% in childhood\(^17\),\(^18\) and 3.5% in adulthood for ADHD\(^19\), and around 1.0% for ASD across the lifespan\(^20\). Despite some decreases of substance use in high-income countries in recent decades\(^21\), substantial groups of individuals worldwide use tobacco, alcohol, and illicit drugs\(^21\),\(^22\). Regular substance use can develop into substance abuse and dependence, with estimates of lifetime prevalence of 24.0% for nicotine dependence\(^23\), 17.8% for alcohol abuse\(^24\), and 7.7% for drug abuse\(^24\). In addition, the prevalence of obesity has increased worldwide in recent decades, with estimates of 15% for obesity (body mass index, BMI ≥ 30 kg/m\(^2\)) among the world’s adult population in 2020\(^25\). Psychiatric disorders, substance use disorders, and obesity are major causes of long-term disability and mortality worldwide\(^26\). Globally, psychiatric disorders contributed to 125.0 million disability-adjusted life years (DALYs), and substance use disorders contributed to 35.1 million DALYs in 2019\(^26\). Likewise, in 2017, high BMI (≥ 25 kg/m\(^2\)) contributed to 70.7 million DALYs in females, and 77.0 million DALYs in males\(^27\).

Individuals with one psychiatric disorder often have a second psychiatric disorder\(^28\),\(^29\). During the lifespan, three-quarters of individuals with MDD develop anxiety\(^28\). ADHD and ASD have an onset in childhood and often co-occur\(^29\),\(^30\). Moreover, family studies have shown increased odds of having depression or anxiety among those with substance use disorders\(^31\),\(^32\). In addition, psychiatric conditions also co-occur with somatic diseases, among which obesity is among the most frequent\(^1\),\(^33\). Increased bidirectional risks have
been reported between depression and obesity\textsuperscript{13}. The co-occurrence of problems yields a higher risk of adverse consequences compared with those for each problem alone, such as sleep problems\textsuperscript{14}, poor health-related quality of life\textsuperscript{1}, cardiac diseases\textsuperscript{15}, greater social and personal impairment\textsuperscript{16}, and elevated rates of suicide attempts\textsuperscript{17}. The co-occurrence of psychiatric disorders, substance use disorders and obesity suggest that these conditions may have a great deal of shared vulnerability, which may be partly explained by shared genetics and shared environment.

**Part 1: Shared genetics in family studies**

Psychiatric disorders, substance use disorders and obesity aggregate within families. Individuals with affected relatives of a specific disease are more likely to develop this disease themselves compared with individuals with healthy relatives\textsuperscript{11,38}. The increased risk effects can be estimated by the recurrence risk ratio ($\lambda_{rr}$), which is the ratio between the prevalence of a disease in relatives of participants with this disease and its prevalence in the general population\textsuperscript{39}. The familial aggregation of a disease may partly be explained by genetic risk. Heritability ($h^2$) is a concept summarizing how heritable a phenotype is and is defined as the proportion of the phenotypic variance attributable to genetic variance\textsuperscript{40}. Genetic variance can be partitioned into additive genetic variance (the additive effects of alleles at each contributing locus), dominance genetic variance (interactions between alleles at the same locus), and epistatic genetic variance (interactions between alleles at different loci)\textsuperscript{40,41}. Narrow-sense heritability is defined as the proportion of phenotypic variance attributable to additive genetic variance\textsuperscript{40}. It is well established that psychiatric disorders, substance use disorders, and obesity are heritable, with heritabilities of 0.37 for MDD\textsuperscript{2}, 0.32 for generalized anxiety disorder (GAD)\textsuperscript{3}, 0.75 for ADHD\textsuperscript{5}, 0.80 for ASD\textsuperscript{5}, 0.57-0.67 for substance use dependence\textsuperscript{5,6}, and 0.46 for BMI\textsuperscript{4}. With a large population-based family design in the Lifelines Cohort Study\textsuperscript{42}, familial aggregation and heritabilities for psychiatric problems, substance use, and obesity will be estimated in this thesis.

Psychiatric disorders, substance use disorders and obesity often co-occur\textsuperscript{1,28-33}. This holds not only within the same person but also within families. For example, individual with a first-degree relative affected with substance use disorder had 1.51 times and 1.66 times higher risk to have depression and anxiety, respectively\textsuperscript{32}. Familial co-aggregation of different problems can, similar to familial aggregation, also be estimated by the recurrence risk ratio, which in this case is the ratio between the prevalence of one specific disease among relatives of participants with another disease and its prevalence in the general population. In turn, the genetic correlation is the correlation between two phenotypes explained by genetic effects, which quantifies the overall genetic similarity between different phenotypes\textsuperscript{43,44}. Genetic correlations suggest shared genetic susceptibility between outcomes and may partly explain the familial co-aggregation of psychiatric problems, substance use and obesity. Genetic correlations estimated from molecular genetic findings are well established\textsuperscript{43,45,46}. However, molecular genetic studies
only capture common genetic variants (i.e., with minor allele frequency >5%), family studies can capture all genetic effects. As the knowledge on familial co-aggregation and shared heritability derived from large family studies is limited, familial co-aggregation and genetic correlations across psychiatric problems, substance use, and obesity will be investigated in this thesis.

**Part 2: Molecular G×E study**

With the rapid development of genome-wide association studies (GWASs) in recent years, thousands of genetic variants associated with complex diseases and behaviors have been identified. Recent genome-wide meta-analysis studies identified 178 independent single-nucleotide polymorphisms (SNPs) for depression, 27 for ADHD, 5 for anxiety, 5 for ASD, 378 for ever smoking, 99 for alcohol use, and 941 for BMI. Most of these SNPs have very small effects, illustrating the polygenicity of these complex traits and diseases. The sum of the number of risk alleles of each SNP as present in an individual, each weighted by the strength of its association with the outcome of interest as found in the GWAS, is calculated as polygenic risk score (PRS), which is used to estimate the degree to which an individual is at risk of disease due to genetic makeup. Based on recent large GWASs, PRSs for psychiatric problems, substance use, and obesity will be calculated in this thesis.

In addition to genetic background, environmental factors have major contributions to disease. For example, it is well known that higher levels of stress and lower levels of socio-economic status show strong associations with poorer mental and physical health. However, it has been insufficiently established to what extent the environment may moderate genetic effects on outcomes of interest (i.e., gene-by-environment interaction, G×E). Previous studies found inconsistent results for interactions between PRS and stress for depression. Both an Australian (n=5,221) and a UK study (n=4,919) found that the PRS for depression had a significant interaction with stressful life events for depressive symptoms, while this was not found in a study from the USA (n=8,761). The interaction between a PRS for BMI and educational attainment was significant for obesity, but not for BMI itself. For substance use, higher neighborhood income amplified the effect of a PRS for alcohol use, while no interaction was found for smoking. So far, the number of studies exploring the interaction between PRS and stress or SES is still limited, and inconsistent findings are likely due to small sample sizes, or to using a PRS based on a still relatively small GWAS discovery sample. With a large sample size and improved PRSs based on recent large GWASs, the interactions between PRSs and a variety of stress or SES indices for psychiatric problems, substance use, and obesity will be investigated in this thesis.

As described, diseases often co-occur, and shared genetic susceptibility might explain part of the co-occurrence. This raises the question whether and to what extent the environment moderates the shared genetic susceptibility for the co-occurrence. To
estimate the shared genetic susceptibility, genomic structural equation modelling (genomic SEM) can be used to investigate shared genetic liabilities across diseases captured as latent broad genetic risk factors in multivariate GWAS\textsuperscript{58}. In recent years, genomic SEM was applied to multiple studies to estimate shared genetic susceptibility and improve our understanding of the shared etiology among psychiatric disorders\textsuperscript{48,58-60}. However, this strategy has so far not been applied to study the potential sharing of G×E mechanisms across conditions, which will be pursued in this thesis.

**Part 3: PRS and family history as predictors of obesity**

Polygenic risk scores have recently become popular in predicting genetic susceptibility to common complex diseases. However, PRSs only capture part of genetic risk (i.e., effects of common genetic variants). The upper bound of the variance explained by PRSs is the so-called SNP-based heritability ($h^2_{\text{snp}}$), which is the proportion of variance in genetic liability associated with common SNPs genome-wide\textsuperscript{61,62}, which usually captures one third to half of the heritability as estimated from behavioral genetic studies in family or twin studies. For example, heritability for BMI was 0.46-0.75 in family/twin studies\textsuperscript{4}, while SNP-based heritability for BMI was 0.28\textsuperscript{53}. As genetic factors are not the only risk factors for diseases and the PRS captures only part of genetic risk, imperfect prediction of an outcome is to be expected\textsuperscript{55}. Family history is typically defined as having at least one first-degree relative with a specific disease and is another important predictor of genetic susceptibility to complex diseases. Family history may capture additional genetic effects as well as shared family environment (e.g., regarding BMI: dietary habits and physical activity\textsuperscript{63}). It follows that when both the individual’s PRS and family history are used, we may improve the prediction of disease.

For parents and offspring, due to random segregation at meiosis, each parent transmits half of their genetics to the offspring, which is captured by the offspring’s PRS. However, non-transmitted alleles in the parents may still influence offspring indirectly, through their impact on parental behaviors\textsuperscript{64}. With regard to obesity, it is currently unknown whether parental obesity phenotypes influence offspring phenotypes, independent of the PRS transmission from parent to offspring. In the present thesis, we will investigate the relative effects of parental PRS (via offspring’s PRS) and parental obesity phenotypes on those of the offspring.

The between-family PRS is the mean sibling PRS, representing the average genetic effect of the family\textsuperscript{65}. The within-family PRS is the difference between the individual and mean PRS, representing individual unique genetic effects\textsuperscript{65}. As siblings have the same ancestry, i.e., the same parents and the same family environment, between- and within-family design among siblings could estimate the effect of PRS free of biases\textsuperscript{66}, such as population stratification\textsuperscript{67}, and assortative mating (i.e., partner selection based on similarities in certain characteristics\textsuperscript{68}). The effect of between- and within-family PRS for obesity will be estimated in this thesis.
Dataset used in this thesis: the Lifelines Cohort Study
Lifelines is a prospective population-based cohort study recruiting over 167,000 participants in the North of the Netherlands between 2006 and 2013. A follow-up second assessment took place between 2014 and 2017. The follow-up third assessment is currently ongoing; it started in 2019 and will be finished in 2023. Lifelines is a multi-generational family-based study, and over 60% of participants have first-degree relatives in Lifelines. Lifelines employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioral, physical, and psychological factors which contribute to the health and disease of the general population, with a special focus on multi-morbidity and genetics. The family structure in Lifelines offers the opportunity to conduct family design studies such as those in Chapters 2 and 3. In addition, among all participants, genetic data of over 50,000 participants are currently available. Chapters 4, 5 and 6 used this genome-wide data to calculate PRSs.

Figure 1. Structure of the thesis
Thesis outline

Aim of thesis
This thesis aims to understand associations between (shared) genetics and environment and psychiatric problems, substance use, obesity, and their co-occurrence. It consists of three parts (Figure 1). In the first part of this thesis, I conduct a traditional family study to estimate the familial co-aggregation and shared heritabilities. In the second part, interactions between genetic risk and environmental factors (i.e., stress exposures and SES) were investigated. In the third part, I combined PRS and family history to predict general and abdominal obesity using between and within family approaches.

Part 1: Family study
Chapter 2 investigates familial aggregation and heritability of depression, anxiety, substance use and obesity, and explores familial co-aggregation and genetic correlations across these phenotypes.

Chapter 3 examines familial aggregation and heritability of neurodevelopmental problems (i.e., ADHD and ASD), and investigates familial co-aggregation and genetic correlations of ADHD and ASD with aggressive behavior, depression, anxiety, and substance use.

Part 2: Molecular G×E study
Chapter 4 examines moderation effects of stress-related exposures on polygenic risk scores for depression and anxiety.

Chapter 5 examines moderation effects of SES on PRSs for depression, anxiety, substance use and obesity, and explores moderation effects at higher aggregated genetic levels for the co-occurrence of these phenotypes.

Part 3: PRS and family history as predictors of obesity
Chapter 6 investigates the relative influence of PRS and family history on indices of general and abdominal obesity using between and within family approaches.
References


Family study