CHAPTER 8
Summary

Psychiatric disorders, substance use, and obesity often co-occur. These conditions not only co-occur within the same individual but also co-aggregate within families. However, the mechanisms underlying this co-occurrence are not fully understood. This thesis aimed to improve our understanding of the associations of (shared) genetics and the environment with psychiatric problems, substance use, obesity, and the co-occurrence of these phenotypes. We used data from the large multi-generational Lifelines Cohort Study conducted in the Netherlands to investigate these aims through three main parts. Firstly, we estimated familial aggregation, co-aggregation, heritability, and genetic correlations of psychiatric problems, substance use, and obesity using the traditional family design (Chapters 2 and 3). Secondly, we investigated the interactions between environmental factors, such as stress exposures and socioeconomic status (SES), and polygenic risk scores (PRSs) for depression, anxiety, substance use, and obesity at both individual and aggregated levels (Chapters 4 and 5). Finally, we combined family history and PRS to predict obesity using between-family and within-family approaches (Chapter 6).

Chapter 2 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 findings showed that depression, anxiety, obesity, and substance use aggregated within families phenotypically and genetically. Similar phenotypic aggregation was also found between spouses. All phenotypes were found to be moderately heritable. Additionally, depression, anxiety, obesity, and smoking showed positive familial co-aggregation, where each conferred increased risk on all the other phenotypes within families, consistent with the positive genetic correlations between these phenotypes.

Chapter 3 estimated the familial (co)aggregation and (shared) heritability of attention-deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) problems, both among themselves and in relation to aggressive behaviour, depression, anxiety, and substance use, using data collected in a subset of the Lifelines Cohort Study (n=37,716). The findings revealed that a high level of similarity was observed within the two subdomains of ADHD and the six subdomains of ASD, with stronger phenotypic and genetic overlap observed within the same disorder domains compared to the cross-disorder domains. Furthermore, ADHD and ASD problems have strong associations with aggressive behaviour at both the phenotypic and genetic levels, and strong associations with depression and anxiety at the genetic level, while displaying weak associations with substance use.

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

Chapter 5 investigated the moderating effects of socioeconomic status (SES) on the association between PRSs and depression, anxiety, substance use and obesity, and explored these moderation effects at higher aggregated genetic levels and aggregated phenotypic outcomes using the genome-wide genotyped data in the Lifelines Cohort Study (n=50,761). The study found that lower SES amplified the effects of PRSs on depression, anxiety, body mass index (BMI), and smoking, while higher disposable income amplified the effect of PRS on alcohol use, with 14 out of 24 interactions proving to be significant. Additionally, lower SES amplified the shared genetic effects on aggregated outcomes. Nine of sixteen interactions investigated between four SES indices (educational attainment, occupational status, household disposable income, and neighborhood SES) and four shared PRSs were significant for the aggregated, latent, depression/anxiety, BMI/waist-hip-ratio, and smoking/alcohol use domains, as well as the latent highest level of aggregation across these three domains. This study provided evidence on the presence of polygenic risk-by-SES interaction effects at, the level of individual PRSs on individual depression, anxiety, BMI, smoking, and alcohol use. Significant interactions were also observed for shared PRS and SES on aggregated outcomes, but with smaller effect sizes, yielding no additional etiological understanding.

Chapter 6 investigated the influences of PRS and family history on BMI, waist circumference and waist-hip-ratio using between-family and within-family approaches in the genotyped part of the Lifelines Cohort Study (n=50,747). The findings revealed that the combination of PRS and family history improved the prediction of these obesity phenotypes. In addition to genetic parent-offspring transmission captured by the PRS, family history, as indexed by parental BMI, waist circumference and waist-hip-ratio, also independently predicted the offspring’s BMI, waist circumference and waist-hip ratio. Similar effects observed for the between-family and within-family PRSs indicated minimal bias, such as caused by gene-environment correlations, in the genetic effects on obesity phenotypes.

In summary, this thesis offered 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 provided evidence for the presence of interactions between polygenic risk and stress exposures in relation to depression and anxiety, as well as interactions between polygenic risk and
SES in relation to depression, anxiety, obesity, and substance use. These studies aimed at finding interaction effects are proof of principle studies: the underlying mechanisms is still unknow. In the study that examined the interaction between polygenic risk and SES, the 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 polygenic risk with family history led to improved prediction for obesity phenotypes. By comparing between-family and within-family results, the study revealed little bias in the genetic estimates for obesity phenotypes. This method could also be applied to other phenotypes, such as depression, anxiety, and substance use, to determine any possible bias.
Nederlandse samenvatting

Psychiatrische stoornissen, middelengebruik en obesitas komen vaak samen voor, niet alleen bij dezelfde persoon, maar ook binnen families. De mechanismen die ten grondslag liggen aan deze clustering worden echter niet goed begrepen. Dit proefschrift heeft als doel om meer inzicht te krijgen in het verband tussen erfelijkheid en omgevingsfactoren in psychiatrische problemen, middelengebruik, obesitas en het samen voorkomen van deze fenotypes. We gebruiken het Nederlandse multi-generationele Lifelines Cohort Study om dit op drie verschillende manieren te onderzoeken. Ten eerste schatten we de familiale aggregatie, co-aggregatie, erfelijkheid en genetische correlaties van psychiatrische problemen, middelengebruik en obesitas met behulp van het traditionele familie onderzoek (hoofdstukken 2 en 3). Ten tweede onderzoeken we de interacties tussen omgevingsfactoren, zoals blootstelling aan stress en sociaaleconomische status (SES), en polygene risicoscores (PRSs) voor depressie, angst, middelengebruik en obesitas, op zowel individueel als geaggregeerd niveau (hoofdstukken 4 en 5). Tot slot combineren we familiegeschiedenis en PRS om obesitas te voorspellen met behulp van inter-familie en intra-familie methodes (Hoofdstuk 6).

Hoofdstuk 2 onderzoekt de familiale (co)aggregatie en (gedeelde) overerfbaarheid van depressie, angst, obesitas en middelengebruik in het multi-generationele Lifelines Cohort Study bevolkingsonderzoek (n=162,423). De bevindingen tonen aan dat depressie, angst, obesitas en middelengebruik fenotypisch en genetisch clusteren binnen families. Vergelijkbare fenotypische clustering werd ook gevonden tussen echtgenoten. Alle fenotypen bleken matig erfelijk te zijn. Daarnaast vertonen depressie, angst, obesitas en roken een positieve familiale co-aggregatie, waarbij elk fenotype een verhoogd risico gaf op alle andere fenotypes binnen families, consistent met de positieve genetische correlaties tussen deze fenotypes.

Hoofdstuk 3 schat de familiale (co)aggregatie en (gedeelde) overerfbaarheid van aandachtstekort-hyperactiviteitstoornis (ADHD) en autismespectrumstoornis (ASS), zowel onderling als in relatie tot agressief gedrag, depressie, angst en middelengebruik, met behulp van gegevens verzameld in een subset van de Lifelines Cohort Study (n=37,716). De bevindingen tonen aan dat er een hoge mate van gelijkenis werd waargenomen binnen de twee subdomeinen van ADHD en de zes subdomeinen van ASS, met sterkere fenotypische en genetische overlap binnen stoornisdomeinen dan tussen stoornisdomeinen. Verder hebben ADHD- en ASS-problemen sterke associaties met agressief gedrag op zowel fenotypisch als genetisch niveau, en sterke associaties met depressie en angst op genetisch niveau, maar zwakke associaties met middelengebruik.

Hoofdstuk 4 onderzoekt de modererende effecten van blootstelling aan stress op de associatie van PRSs met depressie en angst, met behulp van genoombrede gegevens in de Lifelines Cohort Study (n=41,810). De studie toont aan dat verminderinge sociale steun,
hoe hogere blootstelling aan langdurige problemen en stressvolle levensgebeurtenissen, evenals eenzaamheid, de genetische PRS-effecten op zowel depressie als angst versterken. Voor blootstelling aan jeugdtrauma was de interactie met de PRS significant voor depressie, maar niet voor angst. De resultaten van hoofdstuk 4 wijzen op het bestaan van interacties tussen het polygene risico en blootstelling aan stress in relatie tot depressie en angst.

**Hoofdstuk 5** onderzoekt de modererende effecten van sociaaleconomische status (SES) op de associatie tussen PRSs en depressie, angst, middelengebruik en obesitas, en onderzoekt deze modererende effecten op hogere geaggregeerde genetische niveaus en geaggregeerde fenotypische uitkomsten met behulp van de genoombrede gegenotypeerde gegevens in de Lifelines Cohort Study (n=50,761). Uit het onderzoek blijkt dat een lagere SES het effect van PRSs op depressie, angst, body mass index (BMI) en roken versterkt, terwijl een hoger besteedbaar inkomen het effect van PRSs op alcoholgebruik versterkt, waarbij 14 van de 24 interacties significant blijken te zijn. Daarnaast versterkt een lagere SES de gedeelde genetische effecten op geaggregeerde uitkomsten. Negen van de zestien onderzochte interacties tussen vier SES indices (opleidingsniveau, beroepsstatus, besteedbaar inkomen van het huishouden en omgevings-SES) en vier gedeelde PRSs waren significant voor de geaggregeerde, latente, depressie/angst, BMI/taille-heup-ratio, roken/alcoholgebruik domeinen en het latente hoogste aggregatieniveau over deze drie domeinen. Deze studie duidt op het bestaan van interacties tussen het polygene risico en SES op het niveau van individuele PRSs op individuele depressie, angst, BMI, roken en alcoholgebruik. Er werden ook significante interacties waargenomen voor gedeelde PRS en SES op geaggregeerde uitkomsten, maar met kleinere effectgrootte, waardoor geen extra inzicht in de onderliggende oorzaken werd verkregen.

**Hoofdstuk 6** onderzoekt de invloed van PRS en de familiegeschiedenis op BMI, middelomtrek en taille-heup-ratio, door middel van analyses binnen en tussen families in het gegenotypeerde deel van de Lifelines Cohort Study (n=50,747). De bevindingen tonen aan dat de combinatie van PRS en familiegeschiedenis de voorspelling van deze obesitas fenotypes verbetert. Naast de genetische ouder-kind transmissie (bepaald met de PRS), voorspelt de familiegeschiedenis (bepaald met BMI, middelomtrek en taille-heup-ratio van de ouders) ook onafhankelijk van BMI, middelomtrek en taille-heup-ratio van de kinderen. Gelijksoortige effecten die werden waargenomen voor de inter-familie en intra-familie PRSs wezen op een minimale bias, zoals veroorzaakt door gen-omgevings correlaties, in de genetische effecten op obesitas fenotypes.

Samenvattend biedt dit proefschrift inzicht in de familiare co-aggregatie en gedeelde genetica tussen psychiatrische problemen, obesitas en middelengebruik, op basis van een grote familiestudie. Verder onderzoek met geavanceerde genetische methoden is nodig om de mechanismen die deze gedeelde genetica sturen beter te begrijpen.
Het proefschrift levert ook aanwijzingen voor het bestaan van interacties tussen het polygene risico en blootstelling aan stress met betrekking tot depressie en angst, en van interacties tussen het polygene risico en SES met betrekking tot depressie, angst, obesitas en middelengebruik. De studies gericht op het vinden van interactie effecten zijn z.g.n. proof-of-principle studies: het onderliggende mechanisme is nog onbekend. In de studie die de interactie tussen het polygene risico en SES onderzocht waren de interactie-effecten relatief kleiner op het geaggregeerde fenotypische niveau. Dit suggereert dat het modelleren van de genetische en fenotypische overlap van geaggregeerde ziekte-uitkomsten geen extra etiologisch inzicht oplevert. Tot slot toont het proefschrift aan dat het combineren van het polygene risico met de familiegeschiedenis leidt tot een betere voorspelling voor obesitas fenotypes. Door de resultaten van inter-familie en intra-familie met elkaar te vergelijken liet de studie tevens zien dat er geen bias in de genetische schattingen voor obesitas fenotypes is. Deze methode zou ook toegepast kunnen worden op andere fenotypes, zoals depressie, angst en middelengebruik, om mogelijk aanwezige bias vast te stellen.
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About the Author

Rujia Wang was born on March 23, 1992, in Shandong, China. In September 2010, she enrolled in the School of Public Health at Central South University, where she obtained a bachelor’s degree in medicine (majoring in preventive medicine) in 2015. In September 2015, she began her master at Peking University. During her master’s studies, her research focused on exploring the risk factors for HCV and HIV among drug users in China. Simultaneously, she also conducted psychological interventions for amphetamine drug users in Guangdong, China. She obtained a Master of Public Health in 2018.

In October 2018, she initiated her PhD studies under the supervision of Prof. Harold Snieder and Dr. Catharina Hartman at the Department of Epidemiology in the University Medical Center Groningen. During the PhD track, her primary research objective was to investigate associations between (shared) genetics and environmental factors and their influences on psychiatric problems, substance use, obesity, and their co-occurrence using the large multi-generational Lifelines Cohort Study in the Netherlands.

Since December 2022, she has been working as a postdoctoral researcher in Prof. Gerome Breen’s team at King’s College London. During her postdoctoral work, her mainly focus has been on utilizing machine learning to combine multi-family history and multi-polygenic risk scores for predicting depression in the Genetic Links to Anxiety and Depression (GLAD) study. Additionally, she combines genetic data from the UK Biobank and GLAD to conduct severe depression genome-wide association studies (GWAS) and meta-GWAS.
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