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THE GENERAL FACTOR OF PSYCHOPATHOLOGY: PRECURSORS AND CONSEQUENCES

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The general factor of psychopathology: Precursors and consequences

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By

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To all those who love me or have helped me

ABSTRACT

Comorbidity among different types of psychopathology is very common whether they are treated as discrete diagnostic categories or continuous dimensions. Empirical methods to describing these dimensions of dysfunction and their high co-occurrence have advanced our understanding and definition of mental disorders. These methods consistently show that different forms of psychopathology are correlated, resulting in the extraction of a general factor of psychopathology known as the p factor.

In this thesis, we performed multivariate analyses on the nationwide Swedish registers and the Swedish twin registers to examine how the general psychopathology relates to genetics, cardiometabolic complications and pain and suicidal behavior.

In study I, we explored whether psychiatric polygenic risk scores (PRS) could directly predict general and specific psychopathology. We modeled one general and seven specific factors based on childhood psychiatric symptoms, and one general and three specific factors based on adolescent psychiatric symptoms. We then regressed each general and specific factor onto ten psychiatric PRS simultaneously between and within twin pairs, the latter controls for indirect pathways (population stratification, assortative mating and dynastic effects). We found that PRS-general psychopathology associations did not appear attributable to indirect pathways, suggesting that genetics appeared to directly influence symptomatology.

In study II, we examined whether the increased risk of cardiometabolic complications for mental health conditions might be attributed to a general liability toward psychopathology or confounded by unmeasured familial factors. We identified general, internalizing, externalizing, and psychotic factors based on the comorbidity among psychiatric diagnoses and criminal convictions in young adulthood. We then regressed the cardiometabolic complications in middle adulthood on the latent general factor and three uncorrelated specific factors within a structural equation modeling framework in individuals and across sibling pairs. BMI and smoking were used as mediators among child-bearing females. We found that associations between individuals with mental disorders in early life and later long-term risk of cardiometabolic complications appeared attributable to a general liability toward psychopathology. Sibling analyses suggested that the elevated risk could not be attributed to confounds shared within families, and the associations could be partly mediated via lifestyle factors. Clinicians may consider lifestyle-based interventions to reduce the risk of cardiometabolic complications for patients with several mental disorders.

In study III, we investigated the link between chronic pain comorbidity and later suicidal behaviors. Based on nine self-reported chronic pain conditions, we identified three factors related to pain: one general pain factor, and two specific factors, which measure neck-shoulder pain and pain-related somatic symptoms respectively. And we applied a co-twin control model to control for familial confounding when regressing general and specific pain on suicidal behaviors. We found that general pain factor and somatic pain factor are associated with increased risk for suicidal behavior; but these associations appear to be mainly attributable to

familial confounding. Clinicians may find it advantageous to assess pain comorbidity in addition to specific pain types. Nonetheless, addressing pain may not necessarily lead to a reduction in future suicidal tendencies, as the associations may be influenced by familial factors.

LIST OF SCIENTIFIC PAPERS

I. **Chen C**, Lu Y, Lundström S, Larsson H, Lichtenstein P, Pettersson E. Associations between psychiatric polygenic risk scores and general and specific psychopathology symptoms in childhood and adolescence between and within dizygotic twin pairs. *Journal of child psychology and psychiatry*. 2022;63(12):1513-1522.

II. **Chen C**, Chang Z, Kuja-Halkola R, D'Onofrio M. B, Larsson H, Andell P, Lichtenstein P, Pettersson E. Associations between general and specific mental health conditions in young adulthood and cardiometabolic complications in middle adulthood: A 40-year longitudinal familial coaggregation study of 672 823 Swedish individuals. *Submitted manuscript.*

III. **Chen C**, Pettersson E, Summit AG, Boersma K, Chang Z, Kuja-Halkola R, Lichtenstein P, Quinn PD. Chronic pain conditions and risk of suicidal behavior: a 10-year longitudinal co-twin control study. *BMC Medicine.* 2023;21(1):9.

Contents

LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
ADHD	Attention-deficit/hyperactivity disorder
ANX	Anxiety
ASD	Autism
A-TAC	Autism-Tics, ADHD, and Other Comorbidities inventory
ATT	ADHD inattention
BMI	Body mass index
CATSS	Child and Adolescent Twin Study in Sweden
CD	Conduct disorder
CDR	Cause of Death Register
CFA	Confirmatory factor analysis
CFI	Confirmatory fit index
CI	Confidence interval
CON	Conduct
DAGs	Directed acyclic graphs
DEP	Depression
DNA	Deoxyribonucleic acid
DSM	Diagnostic and Statistical Manual of Mental Disorders
DZ	Dizygotic
EFA	Exploratory factor analysis
GEE	Generalized estimating equation
GF	General psychopathology factor
GWAS	Genome-wide association studies
H/I	Hyperactivity/impulsivity
IA	Inattention
IBS	Irritable bowel syndrome
ICD	International Classification of Diseases
IMP	ADHD impulsivity
LD	Learning difficulties
LEA	Learning problems

MBR	Medical Birth Register
MDD	Major depressive disorder
MGR	Multi-generation Register
MZ	Monozygotic
NCR	National Crime Register
NPR	National Patient Register
OCD	Obsessive–compulsive disorder
OR	Odds ratio
PIN	Personal identification number
PRS	Polygenic risk scores
RMSEA	Root mean square error of approximation
SCARED	Screen for Child Anxiety Related Emotional Disorders
SCB	Statistiska Centralbyrån
SDQ	Strength and Difficulties Questionnaire
SEM	Structural equation modeling
SF	Specific factor
SNPs	Single-nucleotide polymorphisms
SOS	Socialstyrelsen
STAGE	Study of Twin Adults: Genes and Environment
STR	Swedish Twin Register
TLI	Tucker-Lewis index
TPR	Total Population Register

1 INTRODUCTION

Recent research has provided compelling evidence that nearly all types of psychopathology show high levels of comorbidity (1). This discovery questions the conventional belief that different diagnoses are independent and unique (2) and instead proposes the possibility of a unified dimension that indicates the risk of developing any form of psychopathology (3, 4). This overlap of psychopathology may be illustrated through a hierarchical model, comprising a general factor of psychopathology at the higher level, which is also known as the "p factor", and specific factors at lower levels, such as externalizing, internalizing, and neurodevelopmental disorders (5, 6). The hierarchical model of psychopathology proposes that various forms of psychopathology can be summarized into a shared factor, akin to the general factor (g factor) observed in cognitive abilities, which explains the positive correlations among scores in intelligence subtests (7, 8). This suggests the existence of a single dimension factor that could account for the inclination to develop any form of psychopathology.

Several research groups have suggested various mechanisms that could potentially account for the theoretical meaning of p factor such as emotion dysregulation, disordered thought, and negative emotionality (7, 9). In addition to evaluating the specific disorder for which an individual seeks treatment, it could be valuable to assess a general factor in psychopathology. The assessment of this general factor may carry significant implications for the choice of treatment approach and prognosis. The therapeutic field has begun to develop manualized treatments for all emotional disorders (10), rather than for specific emotional disorders. It is possible that an even broader set of treatment principles could be developed that partly alleviates all mental disorders. Thus, more need to be learned to further understand the nature of general psychopathology.

Research on behavioral genomics indicates that comorbidity has a partially genetic basis (11-14), and the genetic overlap between different conditions could suggest that genetics are the direct cause of general psychopathology. However, the relationship between genetics and the single dimension of psychopathology needs further investigation as there are potential confounding factors that need to be considered (15), for example, population stratification (16), assortative mating (17), and dynastic effects through parental environments (18).

Psychopathology is individually linked to various adverse health outcomes (19). These associations might be partly due to the latent general and/or specific factors of psychopathology, which well explains the co-occurrence of psychiatric disorders. Additionally, enhanced comprehension of the association between psychopathology and adverse health outcomes could potentially lead to the development of new treatments that target both mental and physical health outcomes (9).

This thesis aimed to bridge the existing gaps in knowledge by examining the precursors and consequences of general psychopathology. The study specifically delved into the potential involvement of genetics in the development of general psychopathology and investigated if there was a direct link between general psychopathology and cardiometabolic complications.

Similar positive correlations among chronic pain conditions are observed (20-24), and chronic pain is considered as a potential risk factor for suicidality (25-28). Understanding the connection between chronic pain comorbidity and suicide is crucial for effectively addressing suicide prevention initiatives. As implied by the hierarchical model that represent the overlap of psychopathology, this thesis also considered overlapping pain conditions via a general factor model and assessed the associations between chronic pain and suicide.

2 LITERATURE REVIEW

2.1 Comorbidity

Currently, the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (29) and the International Classification of Diseases (ICD-10) are used in clinical psychology and psychiatry. They classify mental disorders as categorical, independent, and distinct entities (30). However, comorbidity is a persistent challenge to these systems (31). Comorbidity, which refers to the coexistence of one or more disorders alongside an index disorder (32), has been the focus of extensive research over the past five decades since the term was first introduced. (33). In particular, neglect of comorbidity may cause spurious comparisons when designing and assessing treatment for patients who share the same primary diagnosis. Comorbidity can also affect the clinical trajectory of individuals with identical primary diagnoses by influencing the timing of diagnosis, prognosis, treatment options, and post-treatment outcomes (33).

Recent research based on large samples indicate that comorbidity in psychiatry is highly prevalent (34-38). A study utilizing Danish registers of inpatient and outpatient clinics, spanning almost two decades and encompassing a population of nearly 6 million individuals, demonstrated that receiving a psychiatric diagnosis was associated with significantly elevated risks of a subsequent other diagnoses (hazard ratios range: 2.0, 48.6) (1). Consistent with these observations, a research study, involving 145,990 survey respondents from 27 nations, further revealed a significant level of pair-wise comorbidity (39). Each previous lifetime mental disorder was linked to a higher risk of developing other disorders (hazard ratio range: 5.2, 110.8).

The significant prevalence of comorbidity among mental disorders and symptoms suggests the potential for a more concise classification system than the DSM and ICD (3). That is, because disorders tend to arise in clusters, it might be more efficient to try to directly study these clusters and their precursors and consequences. Furthermore, such a system might benefit clinicians by providing a more reliable measure of overall distress and impairment, which could perhaps even lead to development broader treatment approaches (40-42). In the following section, we will propose that a so-called general factor model might represent a parsimonious way to capture both broad impairment and distress, as well as symptoms that are unique to particular syndromes.

2.1.1 General factor of psychopathology

Achenbach (1966) first used factor analysis to extract higher-order so-called “internalizing” and “externalizing” factors from symptoms in adolescents (43). The internalizing factor primarily consists of anxiety and depression, which directly influence the individual patient, whereas the externalizing factor involves aggressive and delinquent behavior that has an impact on others within the patient's social circle (4). Multiple studies have successfully reproduced these two higher-order factors by examining the pattern of correlations among the first-order dimensions (indicators of psychiatric symptoms or diagnoses) in children, adolescents, and

adults (44-47). Moreover, empirical studies consistently show a strong correlation between internalizing and externalizing factors (48). For example, a study that assessed emotional and behavior problems among 2,190 4–17-year-old youth, found a significant correlation between the internalizing and externalizing factors, with a correlation coefficient of r = 0.54 (47). Likewise, in an US National Comorbidity Survey study (N=8,098; age range, 15-54 years), where mental disorders were analyzed via confirmatory factor analyses, the correlation coefficients between them equaled 0.51 in adults (44). Recently, researchers have suggested that because "internalizing" and "externalizing" factors are so highly correlated, one possibility is that this indicates that they share a common origin, namely a general factor of psychopathology (49).

In the large (N=35,336) and representative NESARC sample, Lahey and colleagues used a bifactor model (50) to show that including a general factor of psychopathology better accounted for the observed comorbidity patterns than Achenbach's original internalizing-externalizing model (4). In a subsequent study, the general factor hypothesis was investigated by analyzing data collected over a span of 20 years, covering the period from adolescence to middle age (3). In this longitudinal study, Caspi and colleagues hypothesized that the data could be accounted for by three correlated higher-order factors: internalizing (including depression, anxiety, and fear), externalizing (including substance use and conduct disorder/antisocial behavior), and "thought disorder" (involving OCD, mania, and schizophrenia). Additionally, they proposed the existence of a general factor based on a bifactor model. The bifactor model, which included a general factor, demonstrated a good fit, comparable to the model specifying three correlated dimensions of psychopathology. However, this finding is conditional on that OCD, mania, and schizophrenia loaded only on the general factor and do not demonstrate independent loading on a distinct higher order "thought disorder" factor. These findings align with the study conducted by Lahey et al. and have formed the foundation for numerous subsequent investigations into the general factor of psychopathology. Since then, several research teams have applied bifactor models to replicate the p-factor across multiple datasets by analyzing measures of psychopathology. (51-55).

More recently, a variety of studies have provided evidence connecting the general factor of psychopathology model with various outcomes such as genetic and environmental factors, treatment approaches, neurobiological problems, personality traits, and outcomes relating to cognitive development, academic performance, distress, self-harm, and suicidality (52, 56-59). Partly based on these associations, researchers have put forth several competing hypotheses to explain the underlying origin of the p-factor, including that it measures nonspecific causal factors (54), dispositional negative affectivity (57), impulsive responsivity to emotion (60), thought dysfunction (55) and broad impairment (61).

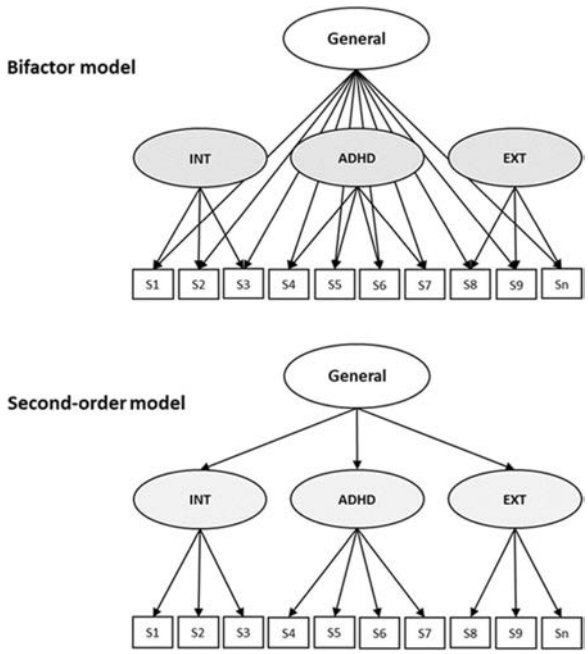
2.1.2 Psychometrics of the general factor model

Although the initial studies identified the general psychopathology factor used bifactor models, there is an alternate model – namely a so-called higher-order model – that can achieve the same goal. As can be seen from Figure 2.1 (6), in the bifactor model, a latent general factor is defined

to capture the shared variance among all indicators, while one or more specific subgroup factors capture additional shared variance within subsets of indicators. The subgroup factors and the general factor are specified to be orthogonal, meaning that they reflect common variance among specific subsets of indicators that can be distinguished from the variance captured by the general factor (50, 62). The higher-order factor model, in contrast to the bifactor model, involves extracting the general factor above the specific subgroup factors (63). This means that the p reflects the variance that the subgroup factors share.

Indeed, the higher-order and bifactor models share mathematical similarities, and the higher-order model can be seen as a more restricted form of the bifactor model (63). Both models make comparable predictions about the covariance among indicators and generally produce similar results. For example, in one study, the two versions general factor model (higher-order and bifactor model) generated highly similar p-factors and predicted alcohol use, suicide attempts, and non-suicidal self-injury similarly well (64, 65).

Figure 2.1 Visual representations of bifactor and second-order models. (Benjamin B. Lahey 2021).



Note. INT – internalizing, EXT – externalizing, S – first-order dimension of symptoms) (6).

2.2 Polygenic risk scores and general factor of psychopathology

The relationship between single-nucleotide polymorphisms (SNPs) and specific traits or diseases are usually examined in genome-wide association studies (GWAS). In the field of genetic discovery research in psychopathology, the primary focus has traditionally been on investigating specific psychiatric disorders by comparing homogeneous cases with healthy

controls (49). Since its inception, this field has placed significant emphasis on expanding sample sizes and refining the phenotypic characterization of individual disorders (49). As a result, multiple large-scale gene identification projects are currently underway, each centering on a specific psychiatric outcome as a qualitative phenotype. This approach is influenced, at least in part, by the pervasive impact of the DSM on the classification of psychiatric disorders (55). However, a narrow emphasis solely on specific psychiatric diagnoses may overlook genetic variants that contribute to susceptibility through shared pathways across different psychiatric outcomes (66).

In fact, a plethora or research indicates that there is considerable genetic pleiotropy such that the same genes increase the risk for several disorders. For instance, family and twin studies provide compelling evidence that each psychiatric disorder has a partly shared genetic origin (2, 67-71). A population-based study (68) utilized national register data encompassing over 3 million full and half-siblings to test the hypothesis a diverse range of psychiatric disorders exhibited a shared genetic influence. The findings provided compelling evidence for the presence of a general genetic factor that impacts various common psychiatric conditions. Which suggests that the identification and exploration of this general genetic factor could serve as a valuable focus for future genetic research in the field.

Molecular genetic studies further demonstrate that different disorders can exhibit overlapping illness-associated genetic variations. This overlap could be attributed to shared gene expression patterns that transcend specific disorders (72-74). Moreover, research utilizing polygenic risk scores (PRS), which involve aggregating thousands of SNPs weighted by their association with cases and controls, has revealed that certain conditions exhibit broader pleiotropic effects. For instance, genetic risk variants identified for attention-deficit/hyperactivity disorder (ADHD) predict a general liability toward childhood psychopathology (75).

While the p-factor seems to have a genetic basis, it's important to consider that genetic associations may also be confounded by familial effects. Confounding factors such as population stratification, dynastic effects, and assortative mating can potentially influence the observed genetic associations (76). Geographic patterns of phenotypes can lead to biased associations between genotype and phenotype if population stratification is not adequately adjusted for (16, 77). Genetic associations can arise as a result of dynastic effects, which involve indirect connections between parental genotypes and the traits exhibited by their offspring, where the family environment that is related to parental genes plays a role in the development of the children's characteristics, rather than the children's own biology (18). Studies indicate that part the parental genotype, which is the portion that children do not inherit, can predict their educational attainment, indicating a passive correlation between genes and environment. The gene-environment correlation contributes to approximately 50% predictive power of the polygenic risk scores (PRS) for educational achievements (18, 78, 79). Assortative mating refers to the non-random selection of partners, which can increase the likelihood of individuals choosing partners who are genetically more similar to themselves, thereby creating genetic correlations between the traits of offspring (80). As there is assortative mating for

mental health conditions, this can potentially introduce bias in the associations between genetics and psychiatric disorders (17, 81).

To address these concerns, one possible solution is to examine the associations between genotype and phenotype in dizygotic twin pairs. These pairs are ideal as they provide a matching mechanism for factors such as population stratification, dynastic effects, and assortative mating, which eliminates the potential influence of familial effects (82-86).

2.3 General psychopathology and later adverse health outcomes

The general factor of psychopathology is significantly associated with life outcomes including psychiatric phenomena and problems with education (58, 87). Since the p-factor captures broad behaviours, so one possibility is that it might also influence health factors associated with lifestyle behaviours. Indeed, there is evidence to support that certain mental health issues experienced during early life have an (inverse) relationship with physical health outcomes in later life. Research suggests that individuals who encounter psychiatric conditions during their youth are at increased likelihood of getting age-related physical diseases as they advance in age (88-91). In a population-based cohort study conducted in Denmark, it was observed that individuals diagnosed with a mental disorder had higher mortality rates compared to those without mental disorders (92). Moreover, a majority of mental disorders were found to be associated with an elevated risk of getting subsequent medical conditions. The hazard ratios for these associations were between 0.82 and 3.62 and were influenced by the duration since the mental disorder was initial diagnosed (93). Likewise, a Swedish population cohort study also suggested patients with youth depression had increased risks of various somatic diseases and of excess mortality, notably, these associations were still significant even after accounting for the comorbidity of other psychiatric disorders (90). Mental disorders such as depressive disorder (94), schizophrenia (95), bipolar disorder (96), and ADHD (97) are also demonstrated to link with high risk of cardiometabolic complications, which in turn increase the mortality rates along with these conditions.

The reason why individuals with mental disorders are more susceptible to developing cardiometabolic syndrome is intricate and multifaceted (98), but lifestyle elements such as smoking, unhealthy eating habits, and insufficient physical activity (99), along with the prolonged use of medication (100-102), have been identified as relevant contributors to the risk.

As noted above, psychiatric disorders often co-occur, which can be captured by a general psychopathology factor (44, 103). This might suggest that the association between mental health problems and cardiometabolic complications might not be entirely specific but also perhaps somewhat attributable to general mental health variation (i.e., a general psychopathology factor).

2.4 Suicidal behaviour and chronic painful conditions

Suicide is the 18th primary cause of death globally, and in 2016, it accounted for at least 1.4% of all deaths (104). The prevalence rates for lifetime suicidal ideation, plans, and attempts in the population have been estimated at 9.2%, 3.1%, and 2.7%, respectively (105). Suicidal behaviours are believed to exist along a continuum, indicating a gradual increase in the severity of suicidal tendencies over time. Research indicates that more than 60% of suicide attempts take place within the initial year of experiencing suicidal thoughts, suggesting a progression from ideation to planning, and eventually, to actual suicide attempts (105, 106). This emphasizes the significance of identifying predictive factors linked to an increased risk of suicide at an early stage.

Multiple studies have indicated a significant association between chronic pain and suicidal behaviours, including thoughts, plans, attempts, and actual deaths from suicide (107-110). Consequently, various clinical guidelines emphasize the need to regard chronic pain as a probably risk factor for suicide (25-28). Similarly, chronic pain has been acknowledged by the World Health Organization as a notable risk factor for suicidal behaviour (111).

However, alike mental health problems, chronic pain conditions also overlap (20-24). Understanding which type of pain is specifically linked with a risk of suicidal behaviour is crucial (112-114). Studies involving twins and genetics have indicated that chronic pain conditions comorbidity can be accounted for by common genetic and environmental factors (115-117). Akin to the general factor of psychopathology, summarizing this pain co-occurrence issue with a general factor model of pain would make it possible to investigate whether suicide is better predicted by general or particular pain.

Moreover, unmeasured genetic or environmental factors could distort the relationship between chronic pain conditions and suicide (118). Therefore, our objective is to explore to what degree the relationships persist after controlling for any unmeasured genetic or environmental factors that are shared within twin pairs.

3 RESEARCH AIMS

The primary objective of this doctoral thesis project was to investigate the relationship between the general psychopathology factor and genetics, cardiometabolic complications, pain, and suicidal behavior.

The specific research questions addressed in each study were as follows:

Study I Do psychiatric polygenic risk scores predict the general factor of psychopathology within dizygotic twin pairs?

Study II Does general psychopathology based on psychiatric disorders in young adulthood predict later cardiometabolic complications?

Study III Do general and specific chronic pain conditions predict later suicidal behavior?

4 MATERIALS AND METHODS

4.1 An overview of the individual studies in the thesis

An overview of the data source, study design, study population, measures and statistical methods used in this thesis is described in Table 4.1.

Table 4.1 Overview of the specific studies in the thesis.

Study	Data source	Study design	Study population	Measures	Statistical methods
I	CATSS	Co-twin control study	3,907 DZ twin pairs aged 9 or 12, a subset 2,393 DZ twin pairs aged 15	Exposure: 10 psychiatric PRS Outcome: 98 parent-reported symptoms in childhood; 20 parent- and self-reported symptoms in adolescence	Bifactor CFA, GEE within SEM framework, Marginal between-within model within SEM framework
II	TPR, MGR, NPR, NCR and MBR	Familial co-aggression study	672,823 individuals born 1955-1962 and their 354,082 non-twin full siblings	Exposure: 8 psychiatric conditions and 2 criminal convictions Outcome: Cardiometabolic complications	Logistic regression, Bifactor EFA, SEM, Mediation analyses within SEM
III	STAGE, NPR and CDR	Co-twin control study	17,148 twin individuals born 1958–1985	Exposure: 9 chronic pain scales Outcome: Suicidal behaviors	Logistic regression, Bifactor CFA, SEM, Fixed effects model

Abbreviations: CATSS, Child and Adolescent Twin Study in Sweden; DZ, dizygotic; CFA, confirmatory factor analysis; GEE, generalized estimating equation; EFA, exploratory factor analysis; TPR, Total Population Register; MGR, Multi-generation Register; NPR, National Patient Register; NCR, National Crime Register; MBR, Medical Birth Register; STAGE, Study of Twin Adults: Genes and Environment; CDR, Cause of Death Register

4.2 Data sources

Since 1947, every individual living in Sweden is assigned a distinct personal identification number (PIN) (119) at the time of birth or immigration. This unique identifier enables researchers to trace people through various demographic registries maintained by Statistics

Sweden (SCB, Statistiska Centralbyrån) and health care registries managed by the National Board of Health and Welfare (SOS, Socialstyrelsen). The present thesis relied heavily on the following national registries as its primary data sources.

Total Population Register

The Total Population Register (TPR) (120) is maintained by Statistics Sweden and records demographic information on all Swedish residents since its inception in 1968. The TPR encompasses data on basic demographics, such as births, deaths, and all migrations in or out of Sweden. To acquire fundamental demographic information, including sex, birthdate, date of migration, birthplace, and marital status, the TPR was utilized.

Medical Birth Register

The Medical Birth Register (MBR) (121) encompasses nearly 98% of all births in Sweden since 1973. It contains maternal information on obstetric history, infertility, diseases, medication use, cohabitation status, smoking and snuff use, self-reported height, and measured weight, which facilitates the calculation of body mass index (BMI).

National Patient Register

The National Patient Register (NPR) (122) was established in 1964 (with psychiatric diagnoses added from 1973) and achieved nationwide coverage of all hospitalizations in Sweden in 1987. In 2001, the register was expanded to include outpatient visits to specialist care clinics. However, it does not include information on primary care visits. The register provides information on the date of admission, discharge, and type of medical specialty involved, as well as any diagnoses and procedures performed. The diagnoses are documented utilizing the period-specific Swedish version of the ICD coding system (ICD-7 1964-1968, ICD8 1969-1986, ICD-9 1987-1996, ICD-10 1997-present), and surgical or medical procedures are registered utilizing the Swedish classification of medical procedures.

Multi-Generation Register

The Multi-generation Register (MGR) (123) holds data on the biological and adoptive connections of all individuals born since 1932, and those who are currently living in Sweden since 1961. The MGR allows for the creation of family pedigrees by associating all inhabitants with their parents.

Cause of Death Register

The Cause of Death Register (CDR) (124) offers data on the primary and contributory causes, as well as the date of all deaths in Sweden since 1952, with complete coverage from 1961. The causes of death are recorded using the ICD coding system.

National Crime Register

The National Crime Register (NCR) (125) comprises information on all criminal convictions in Swedish lower courts, including non-custodial sentences and fines, since 1973. However, no information on criminal convictions for individuals younger than 15 years of age is accessible since this is the legal age of responsibility in Sweden.

Swedish Twin Registry

The Swedish Twin Registry (STR) (126) was created in the late 1950s and comprises data on approximately 200,000 twins who were born in Sweden after 1886. Karolinska Institutet manages the register and when twins reach the age of nine, they are invited to participate in the register. Along with information on zygosity, data from various surveys and biological sample collections are available for several cohorts of twins.

Child and Adolescent Twin Study in Sweden

The Child and Adolescent Twin Study in Sweden (CATSS) (127) is a sub-cohort from STR and focuses on the development of common health and behavioral issues during childhood and adolescence. Starting in 2004, parents or guardians of all twins born in Sweden after July 1995 or between July 1992 and July 1995 were contacted when the twins turned 9 or 12 years old, respectively. The interviews consist of questions about the social environment, general somatic health problems, and a screening tool called the 'Autism — Tics, ADHD and other Comorbidities inventory'. By May 2019, 16,476 parental interviews had been completed concerning 32,952 twins, with a response rate of 69% (126). Recontacts are made with all twins who did not opt out of further contacts at age 15 (twins and parents), 18 (twins and parents), and 24 (twins only).

Study of Twin Adults: Genes and Environment

The Study of Twin Adults: Genes and Environment (STAGE) (126) is a sub-cohort from STR and aimed to screen for prevalent complex diseases and assess relevant exposures during young adulthood and midlife. Between 2005 and 2006, a web-based survey was administered to all twins (a total of 42,582 individuals) born in Sweden between 1958 and 1985. The questionnaire included questions on various common complex health problems and exposures, such as detailed assessments of tobacco use and attempts to quit. The final response rate was almost 60% after combining web and telephone responses.

4.3 Main measures

4.3.1 Psychiatric PRSs

DNA samples collected from participants in the STR study were analyzed using the Illumina PsychChip (126). PRS for ten mental health conditions, including ADHD, ADHD symptoms, major depressive disorder (MDD), autism, eating disorder, schizophrenia, bipolar disorder,

anxiety disorder, post-traumatic stress disorder (PTSD), neuroticism were generated (128). For exposures of study I, P_T≤ 0.50 was used as a SNP-threshold for the analysis (75, 129).

4.3.2 Psychopathology symptoms

4.3.2.1 Parent-reported symptoms in childhood.

In CATSS, when the twins were at ages 9 or 12, their parents used the Autism-Tics, ADHD, and Other Comorbidities inventory (A-TAC) to evaluate their symptoms. This inventory includes 96 items that correspond to symptoms of childhood disorders in the DSM-IV. The questions measure symptoms experienced throughout the twins' lifetimes in comparison to same-aged peers (130). For outcomes of study I, we chose 49 symptoms which evaluated inattention (IA), hyperactivity/impulsivity (H/I), autism (ASD), learning difficulties (LD), and conduct disorder (CD). For those twins born after 1997, CATSS also assessed symptoms of depression and anxiety. The Short Mood and Feelings Questionnaire was used to assess depression symptoms. The questionnaire includes 13 items that correspond child depressive symptoms in the past two weeks (131). Screen for Child Anxiety Related Emotional Disorders (SCARED) was used to evaluate anxiety symptoms. SCARED is a 41-item questionnaire consisting of 41 items that assess symptoms experienced over the past three months. It covers five distinct domains, namely panic, generalized anxiety, separation anxiety, school anxiety, and social phobia (132). For outcomes of study I, we selected 36 SCARED items.

4.3.2.2 Parent- and self-reported symptoms in adolescence.

At the age of 15, both the parents and the twins completed the Strength and Difficulties Questionnaire (SDQ), which is a questionnaire consisting of 25 items that measure conduct problems, hyperactivity, peer problems, emotional symptoms, and prosocial behavior (133). In study I, only the four scales related to problem behaviors were analyzed, and the prosocial scale was excluded.

4.3.3 Psychopathology diagnoses

For exposures of study II, we extracted ICD diagnoses of eight psychiatric disorders (depression, anxiety, alcohol misuse, drug abuse, bipolar disorder, schizophrenia, intentional suicide, and uncertain suicide) between 1973 and 1987 when participants were aged between 18 and 25 years old from NPR. We also included two criminal convictions (violent and property crimes) as they may be related to behavioral disorders, even though they are not considered mental disorders.

4.3.4 Cardiometabolic complications

For outcomes of study II, we extracted diagnoses of cardiometabolic complications from the NPR between 1987 and 2013. These complications included type 2 diabetes mellitus, obesity, hypertensive diseases, hyperlipidemia, and cardiovascular diseases such as ischemic heart diseases, arrhythmia, cardiac arrest, heart failure, cerebrovascular diseases and transient ischemic attack, peripheral artery disease and arteriosclerosis. We excluded individuals who

had both type 1 and type 2 diabetes mellitus to prevent potential confounding effects arising from the presence of two different etiological factors.

4.3.5 Chronic pain conditions

In STAGE, the twins reported various symptoms and indicators of pain using previously validated scales. For exposures of study III, we included nine pain conditions that covered a broad range of pain scales such as chronic widespread pain, irritable bowel syndrome, headaches (including migraines), neck pain, shoulder pain, lower back pain, joint pain, bladder pain, and chronic fatigue syndrome (22, 115, 134-144). We considered each condition as a count of symptoms or severity.

4.3.6 Suicidal behaviors

STR used personal identity numbers to connect the twin participants to records from the NPR and the CDR. NPR supplied data regarding hospitalizations spanning from 1997 to 2016, as well as psychiatrists or other outpatient medical specialists visits from 2001 to 2016. For study III, we analyzed outcomes related to intentional self-harm, including suicide attempts, injuries of undetermined intent, and completed suicides. To identify these cases, we utilized ICD-10 codes (X60-X84, Y10-Y34, Y87.0, Y87.2) from inpatient hospitalizations, visits to medical specialists, and mortality data. In order to capture potential suicidal behavior, injuries of undetermined intent were included in the analysis (145). The register data included the entire population living in Sweden, and the follow-up period lasted for 10 years, extending until 2016, following the STAGE survey conducted between 2005-2006.

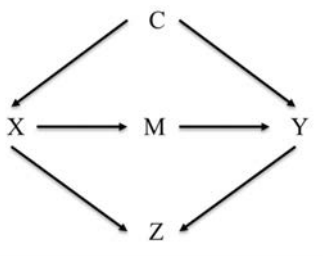
4.4 Study designs

4.4.1 Causal inference from observational studies

Collecting observational data can be done through surveys of a pre-defined population or accessing existing population data like national register linkage or insurance claim datasets. However, this approach carries the risk of biases and confounding variables, which can affect the interpretation of causality. Nonetheless, proper study design and analysis can help in inferring causality, making observational studies a useful alternative to randomized controlled trials. Prior to conducting the study, it is crucial to identify potential confounding factors in order to address both measured and unmeasured confounding from the outset. Researchers can utilize directed acyclic graphs (DAGs) as a visual tool to depict the plausible causal pathways connecting the exposure to the outcome. These DAGs can also incorporate the relevant covariates that exist along the causal pathway, aiding in the understanding of complex relationships. This approach aids in understanding the potential confounding relationships and assists in designing appropriate statistical analyses to account for confounding variables (146). The covariates identified in the DAG can be categorized into several groups based on their relationship to the exposure and outcome. These groups include potential confounders, which are factors that influence both the exposure and outcome; mediators, which are variables that modify the associations between the exposure and outcome; and colliders, which are factors

that are influenced by both the exposure and outcome. These pathways are represented by directed arrows in the DAG (as shown in Figure 4.1). By identifying these covariates, measured confounding can be addressed through statistical adjustment or stratification (147) and unmeasured confounding could be avoid during the study design stage. For example, genetic unmeasured confounding can be accounted for using family-based designs (148).

Figure 4.1 A simplified causal diagram illustrating the relationship between exposure (X) and outcome (Y), a mediator (M), a confounder (C), and a collider (Z).



4.4.2 Genetically informative studies

Genetically informative studies utilize conventional epidemiological techniques within family or relative groups, considering established genetic and environmental connections across family pedigrees. By employing appropriate sampling methods and precise measurements, these designs can effectively address unmeasured confounding factors that may be shared among family members. More generally, genetically informative studies can be applied to a wide range of research questions, such as estimating the heritability of a trait, elucidating the common causes of co-occurring diseases, and assessing the respective influences of genetic and environmental factors on the development of different phenotypes.

4.4.2.1 Co-twin control studies

The co-twin control method is a research design that capitalizes on variations within twin pairs to explore the association between a potential environmental or genetic risk factor and an outcome variable. The method is particularly advantageous for evaluating risk factor-outcome associations by adjusting for unmeasured confounding that are shared within twin pairs, compared to unmatched designs (149). Investigating differences in the relationship between risk factors and outcomes based on zygosity can provide valuable insights. If the risk factor-outcome association is observed only in dizygotic (DZ) twin pairs, it may indicate the involvement of genetic factors in both the risk factor and the studied outcome.

In study I, we estimated the PRS-psychiatric symptom associations within DZ twin pairs. DZ twins share 50% of segregating alleles, and their genetic similarity varies due to the random assignment of alleles during meiosis. However, they are well-matched for factors such as population stratification, dynastic effects, and assortative mating, which reduces potential

confounding influences on the observed associations (15). We measured data on DNA for the PRSs, thus we can use the random differences in PRSs within DZ pairs.

In study III, we estimated the pain-suicide associations within both DZ and MZ twin pairs. MZ twins are 100% genetically identical, both MZ and DZ twins grow up in the same households and experience the same familial environmental factors. When there is a stronger association between an exposure and outcome in MZ twins compared to DZ twins, it suggests that genetic influences may contribute to the observed associations (148).

4.4.2.2 Familial co-aggregation studies

Familial co-aggregation studies explore the clustering of two phenotypes within families to determine if there is a shared underlying cause, known as familial liability, contributing to the observed association between the two phenotypes (150). Different categories of relatives, such as twins, full- and half-siblings, full- and half-cousins, and parent-offspring pairs, can be identified within the population. The familial liability could possibly be decomposed into genetic and environmental components by employing quantitative genetic modeling analysis based on relatives' data. Another common application is to consider familial liability as a potential source of confounding when examining whether the observed association between two phenotypes at the population level is indicative of direct causation or potentially influenced by unmeasured confounders.

In study II, we conducted familial coaggregation analysis to roughly examine the role of unmeasured confounding shared by sibling pairs by regressing the outcomes in the siblings on the latent general and specific factors in the index person (i.e., a cross-trait, cross-sibling association). Familial co-aggregation analysis suggests the significance of genetic and shared environmental factors in understanding the clustering of phenotypes within families. If the cross-trait, cross-sibling associations observed in full siblings remain over 50% (as siblings share 50% of the segregating genes and 100% of the environment), compared to the original within-individual associations. If the cross-trait, cross-sibling associations are less than 50% in full siblings, this indicates either a causal effect or the contribution of non-shared environmental factors. If the cross-trait, cross-sibling associations remain roughly half in full siblings, that is consistent with a genetic etiology. If the cross-trait, cross-sibling associations remain roughly same in full siblings, that indicates shared environmental factors (151).

4.5 Statistical methods

4.5.1 Logistic regression

Logistic regression is a statistical modeling technique used to predict the probability of a binary outcome based on one or more independent variables (152). Logistic regression coefficients represent the relationship between the independent variables (predictors) and the log-odds of the binary outcome in a logistic regression model. Odds ratios (ORs) can then be calculated by taking the exponential of the regression coefficient. In study II and study III,

logistic regression models are used to explore the univariate and multivariate phenotypic associations between the exposures and the outcomes.

4.5.2 Exploratory and confirmatory factor analysis

Factor analysis can be used to analyze the underlying or latent structure of a set of observed variables. Factor analysis helps reduce the dimensionality of the data by representing a large number of observed variables with a smaller number of latent factors. Typically, latent factors are less than the number of observed indicators. This technique is commonly used in the social and behavioral sciences to explore the covariance structures among the observed variables and the latent factors. There are two types of factor analysis: exploratory factor analysis (EFA) and confirmatory factor analysis (CFA). A factor analysis model is formulated as

$$\boldsymbol{y} = \boldsymbol{\mu} + \boldsymbol{\Lambda\eta} + \boldsymbol{\varepsilon} \tag{4.1}$$

Where $\boldsymbol{y}$ implies a $p \times 1$ vector of observed indicators, $\boldsymbol{\mu}$ is intercepts, $\boldsymbol{\Lambda}$ denotes the loading matrix with the element λ_{ij}, $\boldsymbol{\eta} \sim N(\mathbf{0}, \boldsymbol{\Phi})$ implies an $m \times 1$ latent factor, $\boldsymbol{\varepsilon} \sim N(\mathbf{0}, \boldsymbol{\Psi})$ is the disturbance term. The latent factor $\boldsymbol{\eta}$ and the error term $\boldsymbol{\varepsilon}$ are specified to be uncorrelated. Model (4.1) implies the covariance matrix $\boldsymbol{\Sigma}(\boldsymbol{\theta}) = \boldsymbol{\Lambda\Phi\Lambda}^{\mathbf{T}} + \boldsymbol{\Psi}$, where $\boldsymbol{\theta}$ is the estimated parameters. In factor analysis, factor rotations could be done by a set of mathematically specifiable transformations as shown in Equation (4.2) to reposition the latent factors to a new, more interpretable configuration.

$$\boldsymbol{\Lambda\Lambda}^{\mathbf{T}} + \boldsymbol{\Psi} = \boldsymbol{\Lambda}^{*}\boldsymbol{\Lambda}^{*\mathbf{T}} + \boldsymbol{\Psi} \tag{4.2}$$

where $\boldsymbol{\Lambda}^{*} = \boldsymbol{\Lambda}\mathbf{H}^{-1}$, $\mathbf{H}$ is an orthogonal rotation matrix, $\boldsymbol{\Lambda}^{*}$ is the rotated factor loading matrix.

When conducting EFA, researchers usually do not have a substantive theory about which indicators are accounted for by which factors. Instead, the interpretation of the factors is typically inferred after fitting the factor model. As a result, there is no clearly defined model beforehand, and EFA is considered an exploratory technique employed to discover a concise representation of a variable set. On the other hand, CFA follows a similar structure to EFA but incorporates constraints on the parameters. These constraints can include zero loadings, equal loadings, correlated error terms, and restricted factor covariances. These constraints reflect the specific theories that researchers aim to test prior to fitting the model. CFA enables researchers to examine hypotheses concerning the potential relationships between observed variables and latent factors. Researchers begin with a hypothesis that states the anticipated connections between the indicators and latent factors. A CFA model is pre-established based on the underlying theory and/or hypothesis of interest.

4.5.3 Bifactor analysis

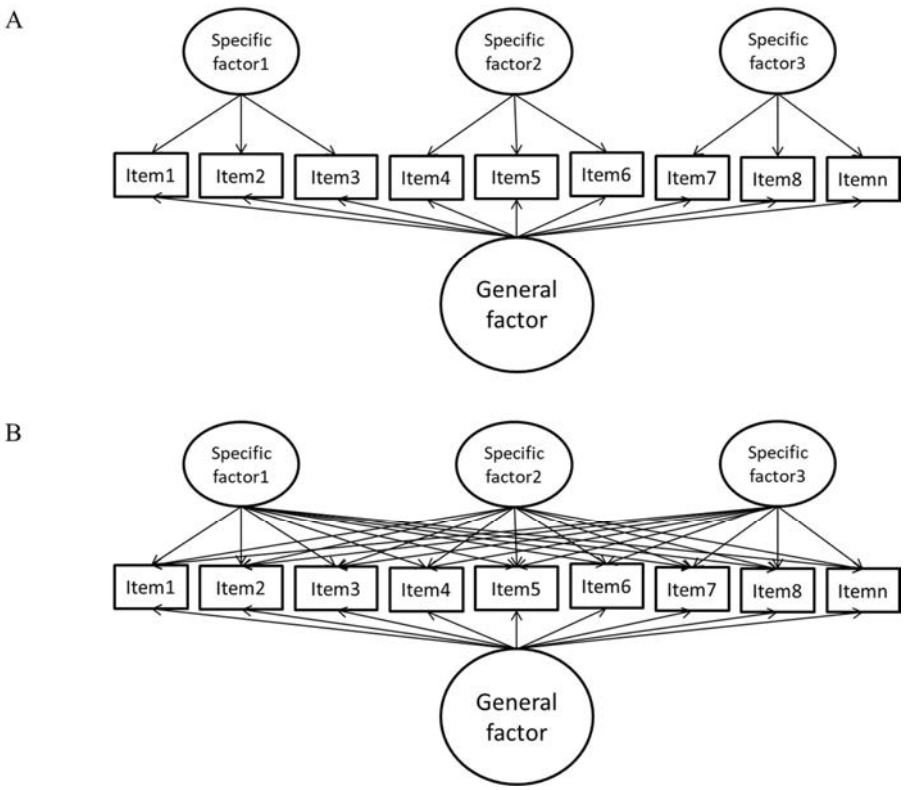
Bifactor analysis (50) utilizes a factor loading matrix $\boldsymbol{\Lambda}$, as depicted in Equation 4.3.

$$\boldsymbol{\Lambda} = \begin{pmatrix} * & * & \mathbf{0} & \mathbf{0} \\ * & * & \mathbf{0} & \mathbf{0} \\ * & * & \mathbf{0} & \mathbf{0} \\ * & \mathbf{0} & * & \mathbf{0} \\ * & \mathbf{0} & * & \mathbf{0} \\ * & \mathbf{0} & * & \mathbf{0} \\ * & \mathbf{0} & \mathbf{0} & * \\ * & \mathbf{0} & \mathbf{0} & * \\ * & \mathbf{0} & \mathbf{0} & * \end{pmatrix} \quad \textbf{(4.3)}$$

In bifactor analysis, the first column loadings are considered as free parameters, while in subsequent columns, at most one free parameter in each row are assumed. The first factor in bifactor analysis is referred to as the general factor, while the remaining factors are referred to as specific factors (Figure 4.2 A). The general factor to captures the shared correlation among the observed variables, while the specific factors account for the unique variance of each variable that is not explained by the general factor. In a bifactor analysis, all of the general and specific factors are assumed to be orthogonal to each other (62), but this requirement is not fundamental (3).

Model building in bifactor CFA involves grouping items based on prior knowledge or information from the field of study. However, there are instances where this prior knowledge may be lacking or incomplete (153). In such cases, exploratory factor analysis with a bifactor rotation criterion can be employed to assist in defining the necessary item groups. One common approach is the second order Schmid-Leiman method which allows a perfect structure for the loadings on the specific factors while loading heavily on the first general factor (Figure 4.2 B) (153, 154).

Figure 4.2 Bifactor CFA model (A) and bifactor EFA model (B).



For study I, we applied bifactor CFA model on the psychopathology symptoms according to the structure of survey scales. To address potential irregular loading structures, we employed the bifactor-(S-1) approach, which involves designating one specific factor as a reference group (155, 156) .

For study II, we used bifactor EFA model instead of bifactor CFA model because it would be unrealistic to hypothesize that psychiatric disorders would strictly align with a single specific dimension in the multivariate situations, whereby they would load at zero on all but one specific latent factor.

For study III, we initially conducted a bifactor EFA on pain conditions since we lacked specific hypotheses regarding the potential covariance between the pain scales. Subsequently, in order to eliminate the possibility of attributing any associations between the specific factors and suicidal behavior to cross-loadings, we specified the EFA-specific factors loading less than |0.30| to be 0. However, since three pain scales (wide, back, and joint pain) exhibited loadings below |0.30| on all specific factors, we adopted the bifactor-(S-1) approach as in study I.

4.5.4 Structural equation modeling

Structural equation modeling (SEM) is a statistical technique used for analyzing multivariate data that allows simultaneous uniting of factor analysis and path analysis. SEM encompasses two fundamental types of models. The measurement model (4.4) articulates the underlying theory that delineates how observed variables are indicators of latent constructs. The structural model (4.5l) portrays the theory that elucidates the relationships between exposures, outcomes, and the latent constructs. The two components of SEM are as follow.

$$\boldsymbol{x} = \boldsymbol{\Lambda}_x\boldsymbol{\xi} + \boldsymbol{\delta}, \boldsymbol{y} = \boldsymbol{\Lambda}_y\boldsymbol{\eta} + \boldsymbol{\varepsilon} \tag{4.4}$$

$$\boldsymbol{\eta} = \boldsymbol{B}\boldsymbol{\eta} + \boldsymbol{\Gamma}\boldsymbol{\xi} + \boldsymbol{\zeta} \tag{4.5}$$

where $\boldsymbol{x}$ and $\boldsymbol{y}$ are indicators, $\boldsymbol{\xi}$ and $\boldsymbol{\eta}$ are latent variables, and $\boldsymbol{\zeta}$, $\boldsymbol{\delta}$, and $\boldsymbol{\varepsilon}$ are error disturbances. Matrices $\boldsymbol{\Lambda}_x$ and $\boldsymbol{\Lambda}_y$ are factor loadings. The matrices $\boldsymbol{B}$ and $\boldsymbol{\Gamma}$ are coefficient matrices, which indicate relations among the latent factors. The latent vector $\boldsymbol{\xi}$ and the disturbances $\boldsymbol{\delta}$, $\boldsymbol{\varepsilon}$, and $\boldsymbol{\zeta}$ are assumed to be uncorrelated of each other. If $\boldsymbol{B}$ and $\boldsymbol{\Gamma}$ are zero, the SEM simplifies to a factor model.

For study I-III, when relating the exposures and outcomes to latent variables, we ran the analyses within an SEM framework. In particular, for Study II, a Direct Schmid-Leiman method was applied for bifactor rotation of measurement model (157), and we integrated this rotation within an exploratory SEM framework. The rotation for the measurement Model (4.5) is shown in Equation (4.2). The other necessary parameter transformations for the structural Model (4.4) be derived with the rotation matrix **H** as shown in Equation (4.6).

$$\boldsymbol{\eta}_{\boldsymbol{rot}} = \boldsymbol{H}\boldsymbol{\eta}$$

$$= \boldsymbol{H} \cdot (\boldsymbol{B}\boldsymbol{\eta} + \boldsymbol{\Gamma}\boldsymbol{\xi} + \boldsymbol{\zeta}) = \boldsymbol{H}\boldsymbol{B}\mathbf{H}^{-1}\boldsymbol{\eta}_{\boldsymbol{rot}} + \boldsymbol{H}\boldsymbol{\Gamma}\boldsymbol{\xi} + \boldsymbol{H}\boldsymbol{\zeta} = \boldsymbol{B}_{\boldsymbol{rot}}\boldsymbol{\eta}_{\boldsymbol{rot}} + \boldsymbol{\Gamma}_{\boldsymbol{rot}}\boldsymbol{\xi} + \boldsymbol{\zeta}_{\boldsymbol{rot}} \tag{4.6}$$

4.5.5 Generalized estimating equation

In observational studies, where measurements are nested within clusters, such as in individuals over time or in family pairs, the correlation between observations must be accounted for to obtain unbiased standard errors. Generalized estimating equation (GEE) is a type of regression analysis that allows for the analysis of correlated data, where observations within the same cluster or group are not independent (158). GEE utilizes the Liang and Zeger sandwich estimator to compute unbiased standard error estimates for regression coefficients. It can handle non-normal residuals and heteroscedasticity in the data by assuming a working correlation structure for the within-subject dependencies, which may not be perfectly specified (159).

For study I-III, we applied sandwich estimator for the analysis of the twin and sibling sample.

4.5.6 Between-within model

Twin data provide a distinct natural resource for accounting for unobserved shared confounders. The between-within (BW) model is a commonly used for analyzing twin data, allowing for adjustment of the confounders (160). A linear between-within model can be expressed mathematically as:

$$E(Y_{ij} \mid X_{ij}, \bar{X}_i) = \alpha_i^* + \beta_w X_{ij} + \beta_B \bar{X}_i \quad \textbf{(4.7)}$$

where i indicates twin pairs, j equals individuals, and we let $X_{ij}$and Y_{ij} are the exposure and outcome, for subject j in cluster i. $\bar{X}_i$ is the mean of the exposure for the given pair, β_w is the within-effects and β_B is the between-effects. The twin cluster-specific intercept α_i^* is usually assumed to normal distributed with constant mean and variance. By including the mean of exposure in the cluster (the between-effect), this model thereby controls for, all cluster-constant confounders (161). For study I, a problem with this model is that when we fix a random effects model for the latent variables with categorical indicators, with the number of factors and the sample size increase, the computational demands of numerical integration become progressively more challenging (162). Sjölander (163) demonstrated that a marginal BW Model (4.8) can be considered as an approximation of the "conditional" BW Model (4.7)

$$E(Y_{ij} \mid X_{ij}, \bar{X}_i) = \alpha^* + \beta_w X_{ij} + \beta_B \bar{X}_i \quad \textbf{(4.8)}$$

where α^* is a fixed intercept, common for all clusters. A cluster robust sandwich estimator is used to handle correlations within twin pairs. This model does not include any random elements and can be fitted quickly.

In study I, we applied this marginal BW model by replacing the outcome part of Model (4.8) with latent variables, thus we ran marginal BW model within SEM framework.

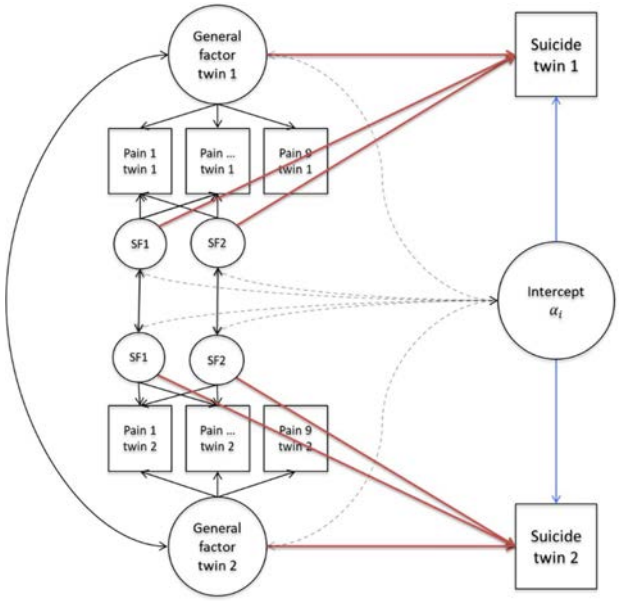
4.5.7 Structural equation model with fixed effects

Fixed effects models allow for controlling variables that have not been measured or cannot be measured. These models consider unobserved differences between individuals as fixed parameters that can be estimated directly or removed from the estimation equations. On the other hand, random effects models treat unobserved differences as random variables with a predetermined probability distribution. The random effects model assumes that α_i (the shared intercept between observations in a cluster i, like siblings in a family) is uncorrelated with the time varying exposures. The fixed effects model accommodates correlations between α_i and the exposures. These additional correlations could be incorporated into SEM by simply specifying the correlations between the latent α_i and the time varying exposures (Figure 4.3) (164).

In study III, we estimated the associations between pain and suicide within twin pairs to control for unmeasured shared confounding using structural equation model with fixed effects (Figure 4.3). Technically, the approach assumes a latent twin-pair intercept α_i and then allows it to correlate with all latent exposures to control for unmeasured shared factors within twin pairs.

If the associations observed among MZ twins attenuate more compared to DZ twins, it suggests the potential exists of genetic confounding (148).

Figure 4.3 A diagram for structural equation model with fixed effects (SF, specific factor).



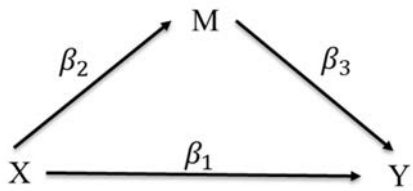
4.5.8 Mediation analysis

The mediation analysis can be performed using different statistical approaches, such as regression-based methods or structural equation modeling (165). The main objective is to examine if the associations between the exposure X and the outcome Y is modified when the mediator variable M is incorporated into the analysis (Figure 4.4). Structural equation modeling offers a versatile and comprehensive framework for conducting mediation analysis. Within SEM, we apply mediation modeling by simultaneously regressing Y on X (coefficient β_1), M on X (coefficient β_2) and Y on M (coefficient β_3) (166). Direct effect of X on Y is measured by β_1; indirect effect of X on Y via M is measured by $\beta_2 * \beta_3$.

If the mediator variable accounts for a portion or the entirety of the association between the exposure and outcomes variables, it is regarded as a significant mediator. This implies that the effect of the exposure on the outcome variable is mediated, either partially or completely, by the mediator variable. Mediation analysis is important because it helps researchers to identify the mechanisms through which an exposure may have an effect on an outcome variable. When conducted with robust prior theoretical knowledge and in the appropriate context, mediation analysis aids in identifying areas of focus for future intervention research. This, in turn, facilitates the development of more effective and cost-efficient alternative therapies (165). In

study II, we included BMI and self-reported smoking among childbearing females as mediators in the analysis.

Figure 4.4 A statistical diagram for mediation analysis with an exposure X, an outcome Y, and a mediator M.



4.6 Ethical considerations

This doctoral thesis included epidemiological research using multiple register datasets. The research fully complies with the ethical requirements for research involving human subjects outlined in the Swedish law (autonomy, justice, beneficence and non-maleficence).

For study I, the participants come from the Child and Adolescent Twin Study in Sweden (CATSS). We got ethical permits for both CATSS 9 (reference number 2010/597-31/1) and CATSS 15 (reference number 2009/793-31/5) form the Stockholm Regional Ethics Committee.

For study II, we obtained ethical approval from the Stockholm Regional Ethics Committee with reference number 2013/862-31/5. The data used in the study was obtained from the Swedish National Registers.

For study III, the participants were sourced from the Study of Twin Adults: Genes and Environment (STAGE). Ethical approval for the study was obtained from the Stockholm Regional Ethics Committee with reference number 2010-322-31/1. In addition to the STAGE data, we also utilized the National Patient Register and Cause of Death Register. Ethical permits for accessing these registers were obtained from the Stockholm Regional Ethics Committee with reference number 2013/862-31/5.

The primary focus in addressing ethical implications within this thesis involved ensuring the preservation of individuals' privacy while handling sensitive personal data. In Sweden, informed consent for register-based research is generally waived (167), thus guiding our approach. To conduct register-based studies, we utilized pseudonymized datasets provided by data custodians such as Statistics Sweden and the Swedish National Board of Health and Welfare. These datasets utilized serial numbers instead of personal identity numbers, which prevented individual information from being linked to specific living or deceased individuals, thereby minimizing the risk of breaching confidentiality. Additionally, privacy protection measures included presenting only aggregated statistics at a group level. Given the potential risks of disclosing identifiable information, particularly in cases involving rare diseases or when combined with detailed information, it was crucial to avoid any potential for individuals to be personally identified within this thesis.

Another consideration is protecting sensitive individual information as we handle the data, meaning that the data should be stored, analyzed and destroyed carefully under laws and regulations documented in the Personal Data Act and General Data Protection Regulation. The learning outcome for the course Good Data Management Practice in Epidemiological Research held at the Department of Medical Epidemiology and Biostatistics guaranteed disciplinary rectitude of the handling of personal data.

5 RESULTS

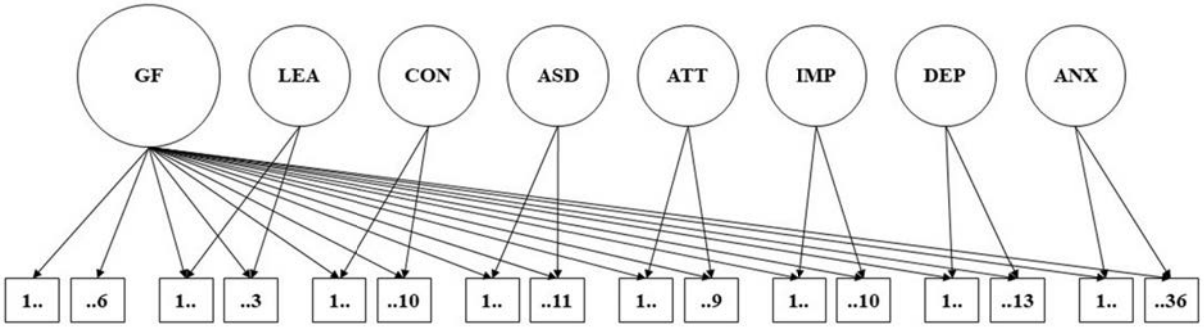
5.1 Study I

In total, we analyzed 3,907 DZ twin pairs aged 9 or 12 (52% male). At age 15, 2,393 DZ twin pairs (49% male) were included in the follow-up.

5.1.1 Bifactor measurement models

The childhood bifactor CFA model, comprising of a single general and seven specific factors (as shown in Figure 5.1), demonstrated a relatively good fit with the data. Likewise, the bifactor CFA model in adolescence, comprising of a single general and four specific factors, also demonstrated a reasonably good fit. The general factor in childhood measured broad psychopathology, with a standardized mean loading of 0.49 (range: -0.03 to 0.80). Similarly, both parent- and self-reported general factors in adolescence also captured broad psychopathology, with standardized mean absolute loadings of 0.51 and 0.40, respectively.

Figure 5.1 Bifactor model of the childhood sample.



Note: Path diagram of the general factor model in the childhood sample. The model consisted of a latent general psychopathology factor (GF) and seven specific latent factors reflecting symptoms dimensions of learning problems (LEA), conduct (CON), autism (ASD), ADHD inattention (ATT), ADHD impulsivity (IMP), depression (DEP), and anxiety (ANX). Variance for all latent factors were fixed at 1. Measured variables are depicted as squares, and include symptoms items from the Autism-Tics, ADHD, and Other Comorbidities inventory (A-TAC), the Short Mood and Feelings Questionnaire (SMFQ), and the Screen for Child Anxiety Related Emotional Disorders (SCARED). Numbers 1…X indicate the number of symptom items loading onto each specific latent trait factor. This figure is reproduced from Chen et al. JCPP 2022.

5.1.2 Latent psychopathology factors regressed on all ten PRSs simultaneously.

For the associations between individuals, we regressed the latent psychopathology factors on all ten PRSs simultaneously, and we also included sex, birth year, and the first six principal components as covariates. Between individuals, as showed in Figure 5.2, the parent-reported general psychopathology in childhood was statistically significantly associated with the PRS for ADHD and ADHD symptoms. Similar results were observed in adolescence (Figure 5.3). Additionally, in adolescence, the PRS for neuroticism was associated with both parent- and self-reported general psychopathology.

Regarding the specific factors in childhood, between individuals, there were statistically significant associations between the PRS for ADHD and specific inattention as well as impulsivity; the neuroticism PRS and anxiety disorders PRS were linked to specific anxiety; the PRS for schizophrenia was associated with specific inattention, learning problems, and autism symptoms; and the PRS for PTSD was associated with specific conduct problems.

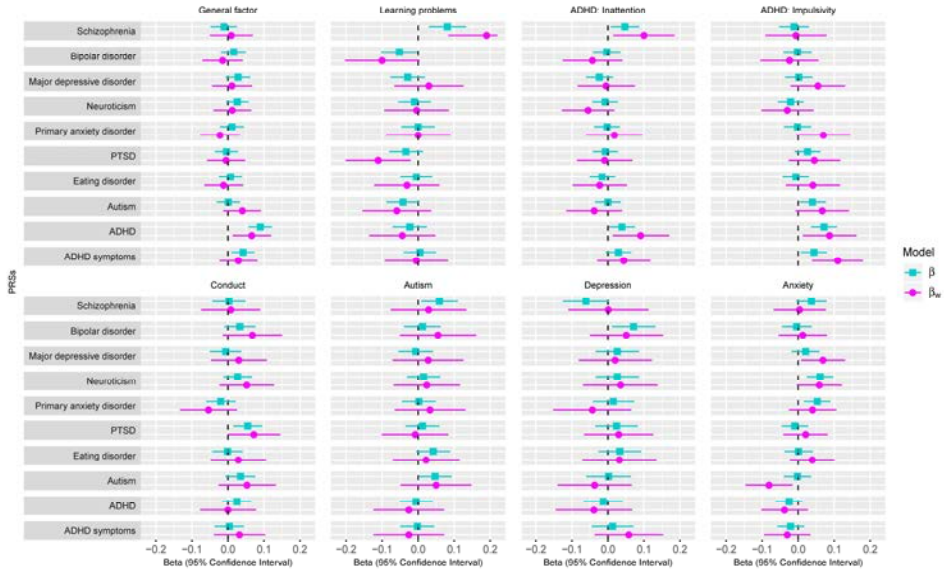
Regarding the specific factors in adolescence, between individuals, the PRS for ADHD was associated with parent-rated specific hyperactivity; the PRS for ADHD symptoms was associated with self-rated specific emotional symptoms; the PRS for eating disorders was associated with self-rated specific hyperactivity and parent-rated specific emotional symptoms; the PRS for schizophrenia was associated with self-rated specific hyperactivity; and the PRS for neuroticism was associated with parent-rated specific emotional symptoms.

For the associations within individuals, the latent psychopathology factors were regressed on all ten PRSs simultaneously within an SEM framework using a marginal BW model by including PRS twin pair means. Within twin pairs (as shown in Figures 5.2 and 5.3), the association between the ADHD PRS and the general psychopathology remained significant in childhood and adolescence. However, in adolescence, there was no longer a significant difference between twins with higher PRS scores for neuroticism and their co-twins.

Regarding childhood specific factors, within twin pairs, the PRS for ADHD remained significantly associated with specific inattention and impulsivity; the schizophrenia PRS continued to be associated with specific learning and inattention problems; the PRS for MDD and autism predicted specific anxiety; and the PRS for PTSD was associated with specific learning problems (Figures 5.2).

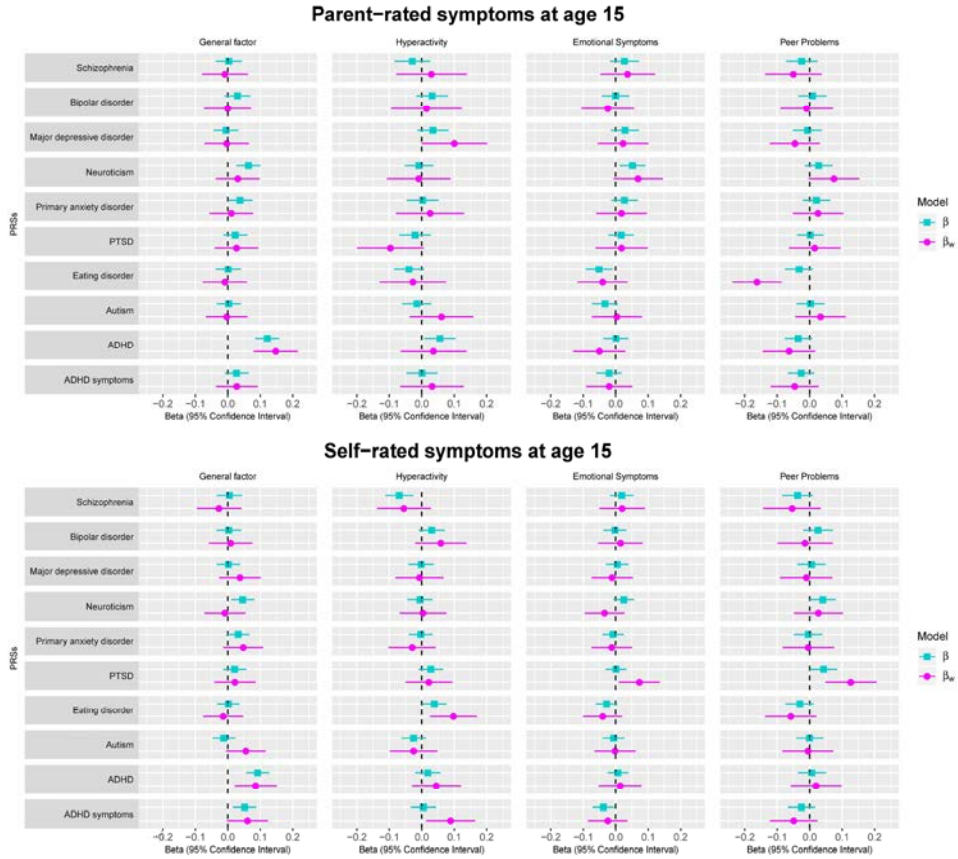
Regarding adolescent specific factors, within twin pairs, the eating disorders PRS was associated with parent-reported specific peer problems and self-reported specific hyperactivity; the PTSD PRS was associated with self-reported specific emotional problems and peer problems; and the ADHD symptoms PRS was associated with self-reported specific hyperactivity (Figures 5.3).

Figure 5.2 Associations between ten PRSs and latent psychopathology factors in the childhood sample.



Note: Between models were adjusted for overlap among ten PRS, birth year, sex and six principal components. Within models were adjusted for overlap among ten PRS, unmeasured confounds shared within DZ twin pairs, and sex. Reported betas are standardized. This figure is reproduced from Chen et al. JCPP 2022 (168).

Figure 5.3 Associations between ten PRSs and latent psychopathology factors in the adolescent sample for the parent-reported and self-reported data.



Note: Between models were adjusted for overlap among ten PRS, birth year, sex and six principal components. Within models were adjusted for overlap among ten PRS, unmeasured confounds shared within DZ twin pairs, and sex. Reported betas are standardized. This figure is reproduced from Chen et al. JCPP 2022 (168).

5.2 Study II

The analysis involved 672,823 individuals (49% females) aged 51-58, along with their 354,082 (non-twin) full siblings.

5.2.1 Bivariate associations between psychiatric disorders and criminality in young adulthood and cardiometabolic complications in middle adulthood

Generally, with the exception of three psychiatric disorders, all other disorders exhibited odds ratios greater than 1.00. Moreover, the majority, except for four disorders, showed statistically significant associations with cardiometabolic complications. The odds ratios for these significant associations ranged from 1.25 to 3.49, as showed in Table 5.1.

Table 5.1 Bivariate associations between psychiatric disorders and criminality in young adulthood and cardiometabolic complications in middle adulthood.

	Outcomes				
	Cardiovascular	Type 2 diabetes mellitus	Hypertensive diseases	Hyperlipidemia	Obesity
Exposures	OR (95% CIs)	OR (95% CIs)	OR (95% CIs)	OR (95% CIs)	OR (95% CIs)
Depression	1.84 (1.62, 2.08)	2.83 (2.39, 3.33)	1.74 (1.53, 1.97)	1.74 (1.41, 2.12)	2.46 (2.06, 2.92)
Anxiety	1.96 (1.74, 2.19)	2.82 (2.40, 3.29)	1.65 (1.47, 1.86)	1.50 (1.21, 1.83)	2.33 (1.96, 2.75)
Alcohol abuse	2.44 (2.19, 2.70)	2.92 (2.51, 3.37)	2.02 (1.80, 2.25)	1.37 (1.12, 1.65)	2.67 (2.23, 3.17)
Drug abuse	2.30 (2.04, 2.59)	3.01 (2.54, 3.56)	1.72 (1.51, 1.96)	0.92 (0.68, 1.19)	2.14 (1.72, 2.64)
Bipolar disorder	0.97 (0.74, 1.25)	2.93 (2.22, 3.80)	1.47 (1.18, 1.81)	1.11 (0.72, 1.62)	1.45 (0.99, 2.04)
Schizophrenia	1.55 (1.28, 1.87)	3.49 (2.79, 4.31)	1.14 (0.92, 1.40)	0.71 (0.45, 1.06)	1.42 (0.97, 1.99)
Suicide intentional	1.86 (1.68, 2.04)	2.47 (2.14, 2.83)	1.90 (1.72, 2.08)	1.86 (1.59, 2.16)	2.45 (2.13, 2.82)
Suicide uncertain	2.02 (1.83, 2.22)	2.32 (2.00, 2.67)	1.78 (1.61, 1.96)	1.71 (1.45, 2.00)	2.21 (1.88, 2.57)
Violent crime	1.59 (1.51, 1.67)	1.87 (1.73, 2.01)	1.42 (1.35, 1.49)	1.30 (1.20, 1.41)	2.03 (1.86, 2.22)
Property crime	1.53 (1.48, 1.58)	1.78 (1.69, 1.87)	1.35 (1.31, 1.40)	1.25 (1.18, 1.32)	1.78 (1.67, 1.89)

Note: Associations were adjusted Sex and year of birth.

Abbreviations: OR odds ratios, CI confidence interval.

5.2.2 Bifactor measurement model of psychiatric disorders and criminality in young adulthood

We applied bifactor EFA analysis on the 10 psychiatric disorders and criminalities and identified one general factor and three uncorrelated specific factors. The general psychopathology factor represents covariance shared among all psychiatric disorders, while the specific factors capture unique covariance specific to subsets of psychiatric disorders, beyond what is accounted for by the general psychopathology factor. All the factor loadings are showed in Table 5.2.

Table 5.2 Exploratory bifactor analysis of psychiatric conditions and criminality.

	Exploratory bifactor analysis			
	General factor	Specific internalizing factor	Psychotic experiences	Specific externalizing factor
Depression	**0.61**	**0.51**	0.16	-0.06
Anxiety	**0.61**	**0.33**	0.28	0.00
Alcohol abuse	**0.73**	0.21	0.09	**0.43**
Drug abuse	**0.72**	0.06	0.18	**0.49**
Bipolar disorder	**0.53**	0.18	**0.44**	-0.09
Schizophrenia	**0.57**	0.13	**0.39**	0.05
Suicide intentional	**0.63**	**0.59**	-0.03	0.06
Suicide uncertain	**0.60**	**0.52**	-0.11	0.19
Violent crime	**0.44**	0.01	-0.18	**0.61**
Property crime	**0.49**	-0.08	-0.13	**0.70**

Note: Loadings equal to or greater than |0.30| are bolded for visual clarity.

5.2.3 Associations between general and specific psychopathology in young adulthood and cardiometabolic complications in middle adulthood

Individual level associations

The general psychopathology factor showed statistically significant associations with all cardiometabolic complications. The odds ratios (OR) for these associations ranged from 1.05 to 1.43 (Figure 5.5). Moreover, the internalizing and externalizing factors were significantly linked to all cardiometabolic complications, whereas the psychotic experiences factor was only associated with type 2 diabetes mellitus.

Familial coaggregation analyses

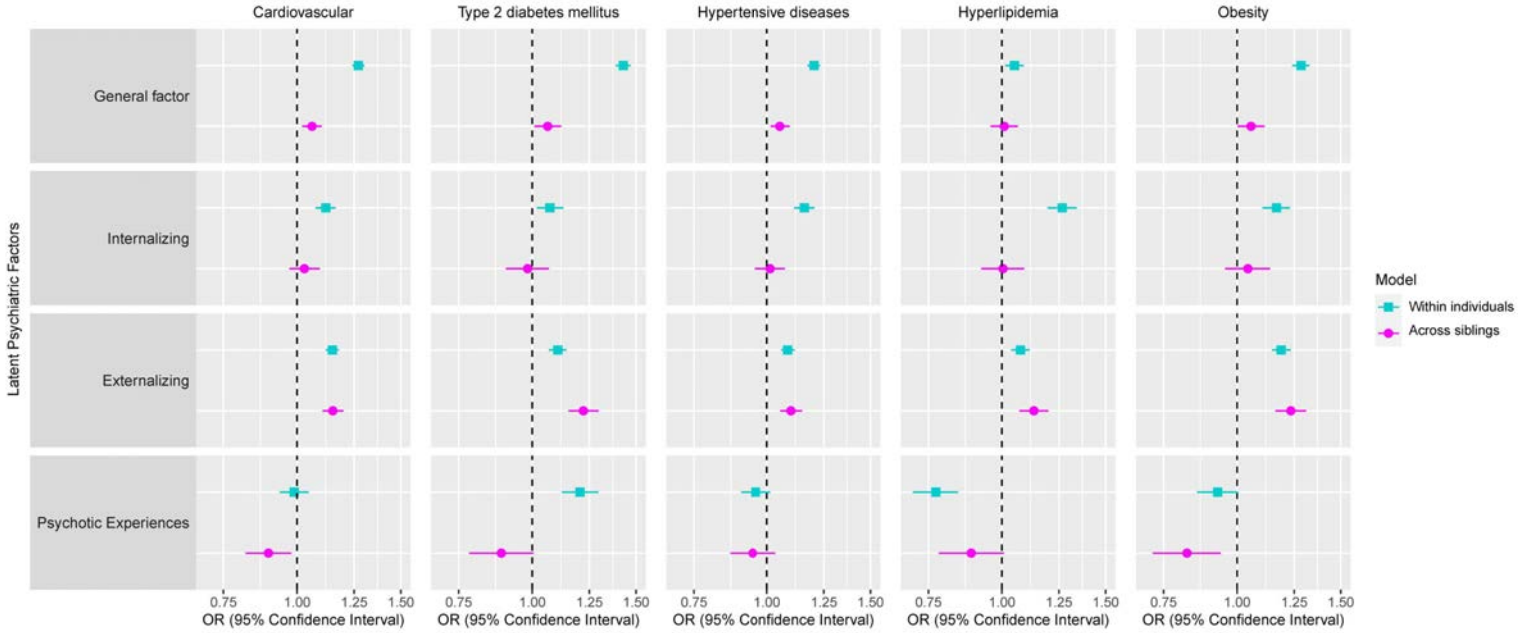
Compared to the individual-level analyses, the associations between general psychopathology factor in the index person and cardiometabolic complications in their full siblings substantially decreased. The odds ratios (OR) for these associations ranged from 1.01 to 1.06 (Figure 5.5). This suggests that the associations were primarily driven by factors that are not shared by sibling pairs. Similarly, the associations between the specific internalizing and psychotic factors in the index person and later cardiometabolic diseases in their full siblings attenuated and became statistically non-significant. However, the associations between specific externalizing factor in the index person and later cardiometabolic diseases in their full siblings

were largely of a similar magnitude as the within-individual associations, indicating the influence of shared effects among siblings, such as childhood socio-economic status.

Mediation analysis

In the mediation analysis, we obtained data on measured BMI and self-reported smoking during pregnancy of 272,473 child-bearing females from the study cohort as mediators. As displayed in Table 5.3 and 5.4, the percent of the association between general psychopathology and each cardiometabolic complication that could be explained by BMI or smoking ranged from 0.7% to 26.6% (on average 6.9%). Similarly, the associations between young adulthood specific internalizing and externalizing factors and later cardiometabolic complications were found to slightly mediated by smoking, but no mediation was observed with BMI.

Figure 5.5 Associations between general and specific psychopathology in young adulthood and cardiometabolic complications in middle adulthood.



Note: The latent psychiatric factors had a mean of zero and a standard deviation of 1. Associations were adjusted by sex and year of birth. Across siblings: regress the outcome in sibling 2 on the exposure in sibling 1.

Abbreviations: OR odds ratios.

Table 5.3 Mediation effects of BMI between psychiatric disorders and later cardiometabolic complications among childbearing women subsample.

	Outcomes				
	Cardiovascular	Type 2 diabetes mellitus	Hypertensive diseases	Hyperlipidemia	Obesity
Exposures	Mediation effects (%) (95% CI)	Mediation effects (%) (95% CI)	Mediation effects (%) (95% CI)	Mediation effects (%) (95% CI)	Mediation effects (%) (95% CI)
General psychopathology	0.7 (-0.1, 1.5)	3.7 (0.8, 6.5)	2.9 (-0.2, 6.1)	6.3 (-0.7, 13.4)	5.2 (0.4, 10.1)
Internalizing factor	0 (-2.7, 2.6)	-0.3 (-13.5, 12.9)	-0.3 (-9.3, 8.7)	-0.5 (-4.9, 4.0)	2.9 (-12.7, 18.4)
Psychotic factor	1.9 (-8.6, 12.3)	6.8 (-9.4, 22.9)	6.2 (-22.9, 35.3)	-4.5 (-16.6, 7.5)	30.3 (-364.2, 424.7)
Externalizing factor	1.1 (-1.1, 3.2)	4.3 (-6.8, 15.4)	8.7 (-8.7, 26.0)	11.1 (-38.2, 60.5)	5.9 (-3.7, 15.6)

Note: Mediation effects = $\frac{\beta_2 * \beta_3}{\beta_1 + \beta_2 * \beta_3}$*100, where outcomes =$\boldsymbol{\beta_1} *$ exposures, BMI=$\boldsymbol{\beta_2} *$ exposures, outcomes =$\boldsymbol{\beta_3} *$ BMI.

Abbreviations: CI confidence interval.

Table 5.4 Mediation effects of self-reported smoking between psychiatric disorders and later cardiometabolic complications among childbearing women subsample.

	Outcomes				
	Cardiovascular	Type 2 diabetes mellitus	Hypertensive diseases	Hyperlipidemia	Obesity
Exposures	Mediation effects (%) (95% CI)	Mediation effects (%) (95% CI)	Mediation effects (%) (95% CI)	Mediation effects (%) (95% CI)	Mediation effects (%) (95% CI)
General psychopathology	7.2 (4.8, 9.6)	5.3 (3.3, 7.3)	7.0 (4.6, 9.5)	26.6 (6.5, 46.8)	3.7 (1.9, 5.5)
Internalizing factor	5.3 (1.3, 9.4)	5.9 (0, 11.7)	4.3 (1.3, 7.2)	4.4 (1.8, 7.0)	2.5 (0.7, 4.4)
Psychotic factor	-0.2 (-6.9, 6.5)	-0.1 (-2.2, 1.9)	-0.4 (-5.4, 4.5)	0.2 (-3.3, 3.8)	-2.7 (-41.8, 36.5)
Externalizing factor	13.7 (5.7, 21.7)	14.8 (3.1, 26.5)	26.7 (-2.3, 55.6)	95.1 (-209.4, 399.6)	5.5 (2.3, 8.7)

Note: Mediation effects = $\frac{\boldsymbol{\beta_2}*\boldsymbol{\beta_3}}{\boldsymbol{\beta_1}+\boldsymbol{\beta_2}*\boldsymbol{\beta_3}}$*100, where outcomes =$\boldsymbol{\beta_1}$ ∗ exposures, smoking=$\boldsymbol{\beta_2}$ ∗ exposures, outcomes =$\boldsymbol{\beta_3}$ ∗ smoking.

Abbreviations: CI confidence interval.

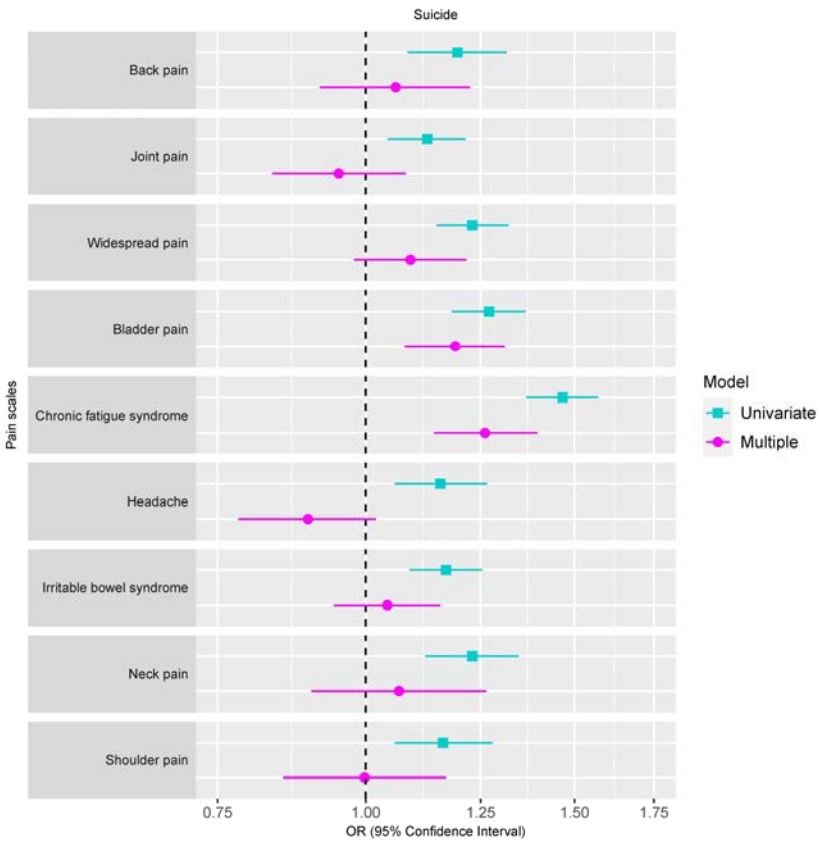
5.3 Study III

This study involved a sample of 17,148 individuals (57% females) aged between 20 to 47 years. Among these participants were 7,126 MZ twins and 10,022 DZ twins. Suicidal behaviors prevalence recorded during the study was 1.6%.

5.3.1 Bivariate associations between pain conditions and suicidal behaviors

The pain conditions increased the risk of subsequent suicidal behavior, as evidenced by odds ratios ranging from 1.13 to 1.47 when estimated separately. Nonetheless, when considering all nine pain conditions in a multiple regression model, only chronic fatigue syndrome and bladder pain exhibited independent associations with suicidal behavior, while other pain conditions did not retain significant associations (Figure 5.6). The observed attenuation suggests that a considerable portion of the associations may be attributed to the presence of broad pain comorbidity.

Figure 5.6 Associations between pain conditions and suicidal behaviors using univariate and multiple logistic regression model.

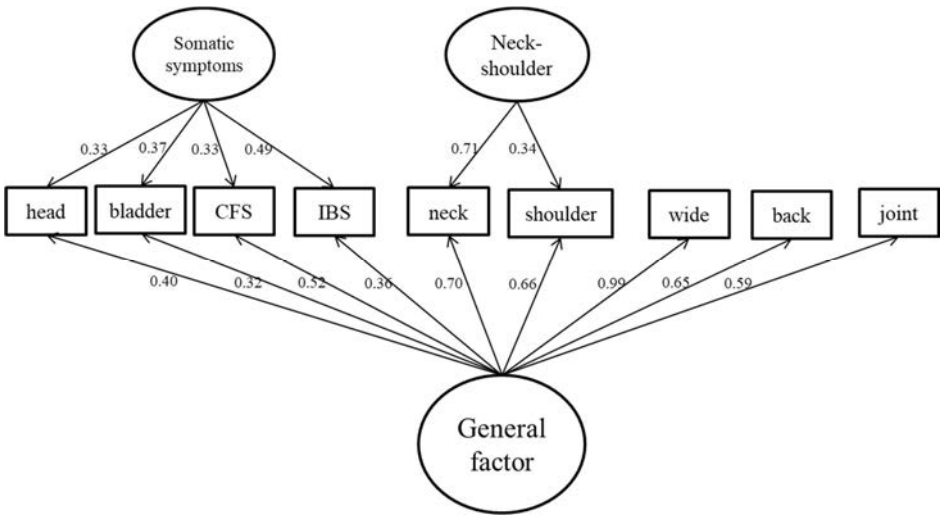


Note: Models were adjusted for age, sex and cancer. This figure is reproduced from Chen et al. BMC Medicine 2023 (169).

5.3.2 Bifactor measurement model based on chronic pain comorbidity

The bifactor CFA model, comprising of a single latent general factor of pain and two specific latent factors reflecting pain dimensions of somatic symptoms and neck-shoulder pain (as shown in Figure 5.7), demonstrated a good fit for the data.

Figure 5.7 Bifactor confirmatory factor analysis model of pain scales.



Note: Variance for all latent factors were fixed at 1. Measured variables are depicted as squares, and include headache (head), bladder pain (bladder), chronic fatigue syndrome (CFS), irritable bowel syndrome (IBS), neck pain (neck), shoulder pain (shoulder), chronic widespread pain (wide), lower back pain (back), and joint pain (joint). This figure is reproduced from Chen et al. BMC Medicine 2023 (169).

5.3.3 Latent general and specific pain factors and suicide behavior

Individual level associations

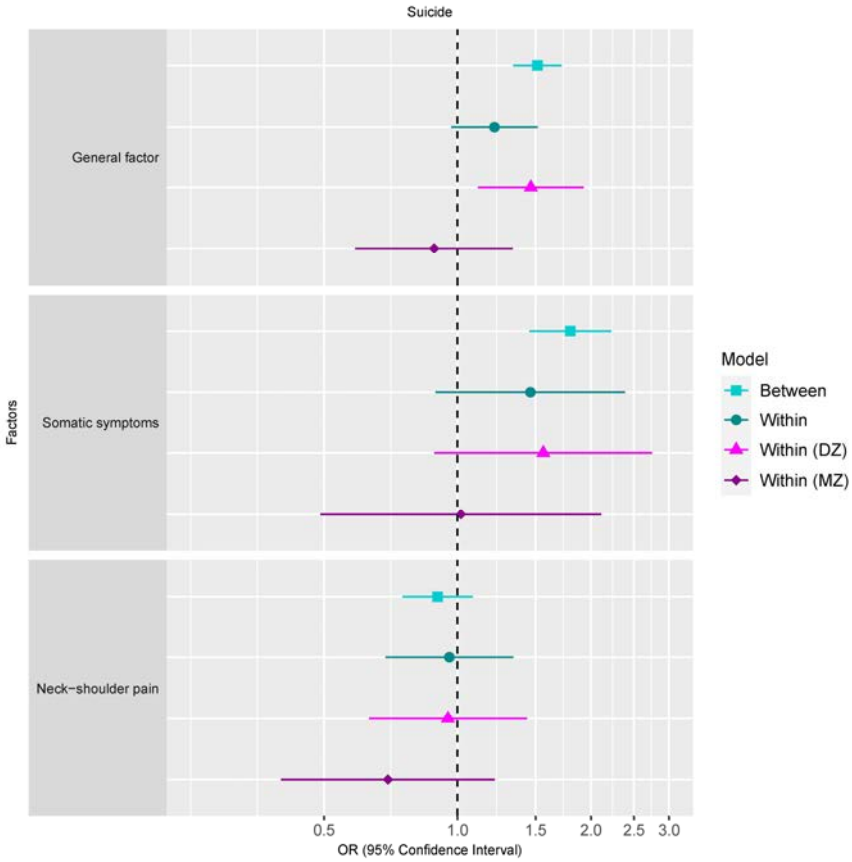
As shown in Figure 5.8, general pain factor increased the risk (OR=1.51, 95% CI [1.34,1.72]) of experiencing later suicidal behavior. Concerning the specific pain factors, the somatic symptoms factor had a statistically significant association (OR=1.80, 95% CI [1.45, 2.22]) with suicidal behavior, whereas the neck-shoulder pain factor did not.

Co-twin control associations (Within-pair associations)

After adjusting for unmeasured confounding shared within twin pairs, the associations between the general pain factor and subsequent suicidal behavior attenuated when both DZ and MZ twin samples were combined. Although this association was statistically significant within DZ twins, it became non-significant within MZ twins (Figure 5.8).

Regarding the specific factors, the somatic symptoms factor was associated with subsequent suicidal behavior between all twins. However, similar to the general pain factor, this association seemed to be solely driven by the DZ twins, as the association was nearly negligible within MZ twins.

Figure 5.8 Associations between latent pain factors and suicidal behaviors between all twin pairs (Model: Between), within all twin pairs (Model: Within), within monozygotic twin pairs (Model: Within (MZ)) and within dizygotic twin pairs (Model: Within (DZ)).



Note: Models were adjusted for age, sex and cancer. This figure is reproduced from Chen et al. BMC Medicine 2023 (169).

6 DISCUSSION

6.1 Psychiatric PRSs and general and specific psychopathology symptoms in childhood and adolescence

Study I examined whether psychiatric PRSs directly influence psychiatric symptoms or through indirect pathways using Swedish twin data. Overall, despite the small effect sizes, some PRSs were significantly associated with the childhood and adolescence general and specific psychopathology symptoms. Furthermore, there was no attenuation in the associations observed within the twin pairs, which indicated that indirect pathways like population stratification, assortative mating, or dynastic effects were unlikely to influence the results.

Between individuals, the PRS for neuroticism was found to predict general psychopathology in adolescence, this is consistent with previous research that has shown neuroticism is a predictor of various mental health conditions and is linked to non-specific variation both genetically and phenotypically (170-173). These associations tended to disappear within twin pairs, potentially indicating the influence of indirect pathways. Within twin pairs, the MDD PRS and neuroticism PRS were found to predict specific anxiety issues during childhood. This is consistent with previous research that has demonstrated that internalizing factor consist of both general distress (depression and generalized anxiety), and specific issues like various phobias (174).

The PRS for ADHD and ADHD symptoms were significantly associated with specific inattention and impulsivity both between and within twin pairs. Additionally, the ADHD PRS was also associated with general psychopathology, which is consistent with earlier research (175). It is worth noting that this association persisted within twin pairs, indicating that impulsivity and inattention could be essential components of a more comprehensive childhood and adolescent impairment and distress. These findings may indicate that impulsive reactions to emotional impulses can explain part of the general psychopathology (176).

The aggregate associations between PRS and the general psychopathology factor were very similar between and within twin pairs, suggesting genetic effects directly influence general psychopathology. However, the associations with the specific psychopathology factors were amplified within twin pairs when examined in the aggregate. This may be simply due to sampling variation or could be due to parents unconsciously comparing their children with each other rather than with same-aged peers (179).

Previous studies have indicated that the relationship between PRSs for education and academic outcomes may be influenced by dynastic effects (18, 79). However, the results of this study suggest that the psychiatric PRSs has a direct influence on the children and adolescents' symptomatology. According to other studies, characteristics that are strongly influenced by the environment that family members share, like education, tend to be more likely to be passed down through families, while traits that are influenced more by genetics and less by shared environment, like psychiatric symptoms, are less susceptible to dynastic effects (78, 83). This

could imply that alleles identified in psychiatric GWAS, compared to those identified in education GWAS, are more likely to reveal underlying biological pathways.

The finding that some PRSs predict both general and specific psychopathology factors suggests that the PRS in GWAS studies may not only contain disorder-specific but also general psychopathology variations (175, 182). If the aim is to pinpoint genetic markers that have a direct impact on comorbidity, it would be advantageous to investigate the genetic makeup associated with ADHD. This is because, among all the PRS examined, ADHD was the only one that displayed a direct association with the general psychopathology factor. If the aim is to identify pathways that are specifically associated with certain disorders, it could be meaningful to separate the genetic variation that contributes to general comorbidity. Multivariate techniques (Genomic SEM bifactor models or conditional GWAS analysis) can be applied to accomplish this (183-185). Additionally, if sampling variation could not explain the amplified within-pair associations with the specific factors, it might be more effective to conduct GWAS studies within sibling pairs when investigating the genetic basis of specific psychiatric disorders. Furthermore, analyzing trios could be useful in exploring the covariance between parental and offspring genetics (76, 186).

6.2 General psychopathology in young adulthood and cardiometabolic complications in middle adulthood

Study II investigated whether mental health and behavior problems in young adulthood would influence cardiometabolic complications in middle adulthood. The results of this study could be summarized into three parts. First, individuals who received any psychiatric diagnosis or had a criminal conviction during young adulthood had higher risk to develop later cardiometabolic diseases. This is consistent with previous research that demonstrated psychiatric disorders were associated with cardiometabolic outcomes (90, 94-96, 187). Second, general liability toward psychopathology contributed significantly to the associations between psychiatric disorders and later cardiometabolic complications, rather than being limited to a specific disorder. Third, the associations between the general psychopathology and later cardiometabolic complications decreased substantially cross siblings compared with the associations within individuals. This suggests that the observed associations could potentially be explained by either a causal relationship or confounders that are not shared among siblings.

Given that unmeasured factors shared among siblings could not explain the associations between the general psychopathology factor and later cardiometabolic complications, it is reasonable to speculate that young adults who experience multiple psychiatric conditions (i.e., higher general factor scores) may engage in unhealthy lifestyles (188). For example, it might be difficult for individuals who suffer from several psychiatric problems to maintain nutritious meals or participate in sufficient physical activity (189, 190). This speculation was further supported by mediation analysis of child-bearing females, where we found that high BMI and smoking explained on average 6.9% (0.7% to 26.6%) of the associations between the general psychopathology factor and later cardiometabolic complications.

Unlike the general psychopathology factor, the associations between the specific externalizing factor and later cardiometabolic complications were approximately at same magnitude both within individuals and cross siblings. This implies that the observed associations could be explained by unmeasured factors shared among siblings, such as socio-economic status during childhood or the environment in which they were raised. This idea is supported by previous research indicating alcohol use and related outcomes were influenced by socioeconomic status (191). Furthermore, a longitudinal study conducted over a period of ten years revealed that both the educational level of mothers and fathers, as well as the educational level achieved in adulthood, have a substantial impact on explaining the risk of cardiovascular diseases in adulthood (192).

From both clinical and public health perspective, findings from this study suggested the importance of considering psychiatric comorbidity in accounting for risk of later cardiometabolic complications rather than examining specific psychiatric disorders and behavioral problems in isolation (49, 193). The findings raise the possibility that transdiagnostic interventions, which are directed at broad psychopathological dimensions, may have greater effects than those directed at individual disorders (194). Currently, there are interventions specifically designed to target underlying mechanisms that are common across various disorders. One example is the unified protocol for transdiagnostic treatment of emotional disorders (194). Broadly speaking, our findings suggest that clinicians may consider lifestyle-based interventions when treating patients with multiple psychiatric conditions to prevent later cardiometabolic complications.

6.3 Chronic pain comorbidity and risk of suicidal behavior

Study III examined whether self-reported chronic pain conditions could predict clinically assessed suicidal behavior using nationwide Swedish twin data. The findings of our study revealed that experiencing chronic pain conditions were linked to a higher risk of experiencing suicidal behavior in later life. Nevertheless, when we accounted for other pain conditions in a multiple regression analysis, only a limited number of associations remained statistically significant. This pattern of results obtained from the univariate and multivariable analyses is in line with prior research that has faced challenges in identifying whether the risk of suicidal behavior is specific to one pain condition or due to multiple pain conditions (108, 110, 195). And these results implied that a shared liability might explain the observed associations between chronic pain conditions and risk of suicidal behavior. This hypothesis was tested by exploring general and condition-specific processes and we found that the general pain factor significantly predicted suicidal behavior, as well as specific somatic symptoms factor.

The findings from our study are in line with prior research, which demonstrated a link between non-cancer pain conditions (pain intensity) and a higher risk of suicidal behaviors after controlling for known confounding, such as mental health conditions (196-200). Although efforts have been made to control for confounding through measured covariates (201), bias from residual confounding threaten the understanding of the causal processes underlying these associations (112). We applied a co-twin control study to control for shared unmeasured

confounding (202, 203), expanding previous pain and suicide studies. The co-twin control design adjusts for all unmeasured or known factors that are shared within twin pairs in the early environment or upbringing. Moreover, we assessed the associations using latent pain factors, which should be free of measurement error compared with the direct associations between pain diagnoses and suicide.

By utilizing a study design that is arguably more robust, we observed results that were different from previous findings: A general factor of pain was linked to suicidal behavior in DZ twins, but not in MZ twins. Similar observations were found with regard to the specific somatic symptoms factor. Our findings imply that the relationships between pain conditions and suicidal behavior may be attributed, to some extent, to shared genetics instead of a causal impact of general or specific pain liability on subsequent suicidal behavior.

The results from our study imply that treating pain may not be sufficient in reducing risk of later suicide. It's important to note that, beyond this non-causal interpretation, there are two possible explanations for the attenuation observed. One possibility is that genetics could influence both pain and suicidal behavior, with pain serving as a mediator of this association. However, this explanation is deemed unlikely given that non-shared environmental factors are not adjusted for in the co-twin model, and any remaining twin pair differences should still be associated with suicide. Another possibility is that the null association is due to low statistical power or pain measurement error, although the study attempted to limit measurement error through the use of a latent factor model. Despite this, the results of this study repeated prior findings that pain conditions increased the risk of suicidal behavior. Therefore, it is still recommended to apply suicide screening and suicide-specific interventions in this population with chronic pains, even if the pain conditions do not directly increased risk of suicidal behavior.

The different associations observed between the DZ and MZ samples indicated the causal influence of pain to suicide could be confounded by the shared genetic factors. We find these explanations to be credible, given the existence of genetic influences on both general pain liability and suicide (116, 117, 204, 205). It is possible that genetic effects on the endogenous opioid system may explain the co-occurrence of chronic pain and suicidal behavior to some extent (206). Numerous studies have established a link between chronic pain and other mental health disorders beyond suicide, indicating the presence of shared genetic factors (115, 117, 207, 208).

In contrast to previous studies that have employed multiple regression models to account for comorbidity among chronic pain conditions, we utilized a novel bifactor analysis to condense the correlations into a single general pain factor and two distinct specific factors (i.e., somatic symptoms and neck-shoulder pain). Shared genetic, neurobiological, and psychosocial factors have been suggested as potential explanations for the comorbidity observed among various chronic pain conditions (116, 117, 209). This suggests that to fully understand the relationship between specific pain syndromes and outcomes like suicidal behavior, it's essential to consider broader underlying processes. The bifactor methodology provides a way to address this issue.

Our findings indicate the possibility of a general factor that explains substantial variability across major pain syndromes, which could be beneficial for clinicians in designing treatment strategies and forecasting pain prognosis.

Aside from the general pain factor, we also identified two additional factors that account for the correlations among specific pain conditions. The first factor, somatic symptoms, may represent an alternate cause for symptoms besides musculoskeletal pain. The second specific factor corresponds to neck and shoulder pain, which could suggest injury or other causes in these regions. However, we did not observe any association between neck- and shoulder-specific pain and the risk of suicidal behavior.

Our study findings suggest that individuals experiencing chronic pain have a higher risk of suicide, although the chronic pain might not be a significant contributing factor. Future research could consider investigating other specific chronic pain conditions (vulvodynia, migraine, temporomandibular disorder，or other chronic headache conditions). Additionally, studies could include more chronic and/or severe pain measures, identify risk factors for suicide among individuals with chronic pain, and evaluate interventions aimed at reducing suicide risk in this population.

6.4 Methodological consideration

6.4.1 Control of confounding

Study designs, such as co-twin control study, can help to control for the shared confounding, however, there are still some factors that could confound the effects. For study I, although the analyses conducted within twin pairs accounted for passive gene-environment correlation, they failed to consider active or evocative gene-environment correlations, which may become more significant as individuals grow from childhood to adulthood (210). For study II, familial co-aggregation analyses evaluated the role of shared confounders between siblings. But we cannot completely exclude the possibility that the observed associations may still be influenced by factors that are not shared between siblings (203). For study III, co-twin control design adjusted for shared familial confounding within twins. However, it is important to acknowledge that there may still exist confounding factors within twin pairs, such as psychopathology or other potential factors (196).

6.4.2 Selection bias

Study I and III conducted a cohort study of Swedish twins based on survey sample. There is a possibility of selection bias due to varying participation rates in the CATSS and STAGE surveys, as well as the completion rates for the survey scales (211). If the responders and non-responders differ on the estimates of interest, characteristics of responders and non-responders should be used to adjusted for the bias.

6.4.3 Generalizability

The generalizability of the findings in this thesis may be constrained by the following factors. For study I, the small effect size and large standard errors due to lack of statistical power made it difficult for us to compare the between and within associations. Therefore, it is still important to replicate these analyses in separate and unrelated samples, to determine if the same association patterns will emerge.

The findings of study II were limited in their generalizability due to the reliance on registers that typically capture more severe cases. The indicators used in this study were based on treatment-seeking behavior or criminal convictions, which means that the results cannot be applied to individuals who do not seek treatment or are not convicted of illegal behaviors. Additionally, the mediation analyses were conducted only with data from females, leaving it unclear whether the results would apply to males. Another potential limitation is that smoking behavior was only recorded during pregnancy, which may have been subject to under-reporting. Finally, the study did not have comprehensive measures of other important mediators such as medications and physical activity.

For study III, we relied on the nationwide register-based data to examine clinically recognized suicidal behavior, however, it's important to acknowledge that some suicidal behavior may not be included in the clinically diagnoses and therefore wouldn't be included in the register data. To improve this limitation, we included injuries of undetermined intent as the suicide outcome. We also included deaths by suicide as the diagnosed suicidal behavior, nonetheless, it's worth noting that there may be differences in the etiologic causes between suicide attempts and deaths (212).

7 CONCLUSIONS

I. The psychopathology symptoms during childhood and adolescence are primarily predicted by genetics. Nevertheless, these associations may differ when relating to general and specific psychopathology.

II. People who have mental or behavioral issues, regardless of type, have a greater chance of developing cardiometabolic complications. Since these associations seem not to be attributed to familial factors, transdiagnostic interventions may be effective in decreasing the risk of future cardiometabolic complications.

III. General and somatic pain were linked to suicidal behavior independently. However, these links were weakened and no longer significant within MZ twin pairs. Clinicians may find it useful to assess not only specific types of pain but also comorbid pain. Nevertheless, treating pain may not necessarily reduce the risk of future suicidal behavior.

8 POINTS OF PERSPECTIVE

This thesis has used genetically informative studies (co-twin control and familial coaggregation design) and based on nationwide Swedish registers and the Swedish twin registers to explore the precursors and consequences of the general psychopathology. Findings presented in this thesis emphasized that genetics could directly predict general psychopathology, as well as that general psychopathology was associated with adverse physical conditions (cardiometabolic complications). And chronic pain comorbidity measured by general pain factor was linked to suicidal behavior. Nonetheless, further research should be continued to improve the clinical implications of the general factor of psychopathology/pain.

To better understand the general factor model of psychopathology, it is imperative to initially examine its structure, reliability, and stability. The general factor model demonstrates considerable robustness as it has been consistently replicated across diverse samples. It effectively captures the underlying structure of psychopathology across various age groups, employing a range of measurement techniques such as diagnoses, symptom counts, and continuous questionnaire measures. Moreover, the model encompasses multiple perspectives through self-report and parent report assessments (213). Numerous studies have indicated the high temporal stability of general factor scores across different developmental stages. Specifically, research has demonstrated notable stability in childhood (214) , adolescence (52, 215), and adulthood (216). However, it should be noted that while the general factor remains consistent, certain specific factors may exhibit comparatively lower stability during adulthood or during the transition from adolescence to adulthood (6). Besides, the symptoms and disorders varied across assessment occasions, which could lead to an underestimation of the true stability (217, 218). In addition, these studies examined the stability of the general factor across only a couple of years, such that it remains unknown whether the stability remains high across several decades. To comprehensively understand of the stability of various factors of psychopathology over time and throughout different stages of life, further studies are warranted. These studies would contribute to identifying the factors that impact this stability and provide insights into the dynamic nature of psychopathology (14).

Second, from clinical perspective, different disorders often response to the same treatments, but whether a transdiagnostic approach based on the general psychopathology could benefit treatment for boarder psychopathology and relating life impairments is still in theory. Moreover, establishing whether psychotropic medication is responsive to influence the general factor would provide a strong rationale for psychological interventions. Future research will be critical for guiding clinical decisions and improving the overall effectiveness of mental health treatments.

Third, the findings presented in this thesis indicate the presence of a factor that explains significant variance across chronic pain conditions. However, as has been pointed out in relation to the general factor of psychopathology, evidence supporting the summarize of positive intercorrelations among chronic pain conditions into a general latent factor still need

to be examined. It would be very useful for future studies to repeat he present analyses using different samples, especially exploring the relationship between pain comorbidity and other adverse life outcomes.

9 ACKNOWLEDGEMENTS

Being able to pursue a PhD at Karolinska Institutet is a tremendous honor, and I am deeply grateful for this opportunity. Throughout my journey, I have been challenged in ways that have pushed me to grow both personally and academically. I owe a debt of gratitude to people who have generously supported me along this way - their guidance, mentorship, and encouragement have been instrumental for me.

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