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THE DEVELOPMENT OF PSYCHIATRIC DISORDERS AND ADVERSE BEHAVIORS: FROM CONTEXT TO PREDICTION

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The Development of Psychiatric Disorders and Adverse Behaviors: From Context to Prediction
THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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POPULAR SCIENCE SUMMARY OF THE THESIS

Psychiatric disorders are common syndromes that impact a person's behavior, emotion, or ways of thinking. Each year, 20% of adults and 17% of adolescents meet the criteria for a psychiatric disorder in the United States. However, despite their prevalence they are often taken less seriously than physical illnesses and stigmatized. So, it is important to learn what developmental aspects are linked to psychiatric disorders to understand patients and support prevention.

One avenue for prevention is to use prediction models to identify people who are at the highest risk of developing a psychiatric disorder for follow up with a doctor. Prediction models, also called machine learning models, are computer programs that work by "learning" from one data set and then predicting a new data set. Researchers manually change parts of the program called hyperparameters to help the model "study" the data set. Prediction models are relatively new in psychiatric research, so there is still uncertainty on how to best apply them.

This thesis aims to understand I.) the developmental aspects that are associated with developing a psychiatric disorder and II.) prediction modeling methods, which could help identify those at risk for developing a psychiatric disorder.

Study I investigated the association between type 1 diabetes (T1D) and eating disorders in Sweden and Demark. First, we found that children and adolescents diagnosed with T1D had twice the risk of being diagnosed with an eating disorder compared to those without T1D. Regarding familial association, we did not find stable evidence that having a family member with T1D increased the risk of being diagnosed with an eating disorder. That said, people with a sibling with T1D had a higher risk of being diagnosed with an eating disorder in Sweden but not Denmark. Our results suggest that the link between having T1D and an eating disorder is not driven by genetic factors, but rather from something else related to the two disorders. One

hypothesis is that people with T1D have to monitor their food closely, which may lead them to use food as a coping mechanism.

Study II examined borderline personality disorder (BPD) in great detail. BPD is a serious psychiatric disorder that affects 2% of the global population. Symptoms include mood swings, unstable romantic relationships and friendships, and fear of abandonment. Being diagnosed with BPD has been associated with many different psychiatric disorders, physical illnesses, traumas, and behaviors that harmful to oneself or others.

We found that having BPD was associated with nearly all of the psychiatric disorders, physical illnesses, traumas, and behaviors that we examined. For example, being diagnosed with BPD was highly associated with being diagnosed with bipolar disorder, post-traumatic stress disorder, and epilepsy. Additionally, people diagnosed with BPD had higher instances of experiencing any type of trauma (for example, being the victim of a violent crime).

The main goal of **Study III** was to create a prediction model that could predict who would have high levels of psychiatric symptoms at age 15 based on data from when they were 9 or 12 years old. The best performing prediction model was able to predict who would or would not have a high level of psychiatric symptoms at age 15 reasonably well, but would not be useful in a psychiatric clinic. The model was correct only 16% of the time when it said that a person would have psychiatric symptoms, whereas it was correct 96% of the time when it said a person would not have psychiatric symptoms. As to which model performs best, we found that there was not a difference between any of the model types, meaning that researchers do not need to use complicated techniques for studies with similar goals.

Study IV set out to build a prediction model that could predict if teens would harm or think about harming themselves (suicidal behaviors), be aggressive, or both by age 18. The model was able to determine if an individual would have suicidal behaviors, aggressive behaviors, both, or neither to some extent. We used two datasets to check if the model was generalizable

to Northern Europe. In the Swedish data set the model was correct 35% of the time it placed a participant into a category and correct 80% of the time it did not place a participant into a certain category on average. In the Dutch data set it was correct 30% and 81% of the time respectively. Finally, we found that the genetic variables we included were useful to the model, meaning that future researchers and clinicians can still make use of this type of data when they combine it with other data types.

To conclude, this thesis details a few of the background factors and negative outcomes that are common with the development of psychiatric disorders and highlights the current limitations of prediction models. We found many relevant findings of use to researchers and clinicians. First, eating disorders and T1D are linked, but probably not because of genetic factors. Second, being diagnosed with BPD is associated with many health conditions, trauma, and negative behaviors. Third, it does not matter which type of prediction model researchers use if their data and questions are similar to those we used. Finally, while genetic information is not helpful for psychiatric clinicians on its own, it can be when used with other types of data. Together, the results show the hardship associated with treating, predicting as well as being diagnosed with a psychiatric disorder. In light of these findings, empathy and advocacy is needed for people who have symptoms of a psychiatric disorder.

ABSTRACT

Psychiatric disorders by definition cause significant impairment in an individual's daily functioning. Certain disorders, such as borderline personality disorder (BPD) and eating disorders, have worse prognosis and high mortality rates compared to other psychiatric disorders. Similarly, adverse behaviors such as self-harm, suicide, and crime are often present in individuals with psychiatric disorders. It is of interest to further understand the etiology and associations of BPD and eating disorders to uncover potential avenues and opportunities for intervention. Moreover, prediction modeling has recently come of interest to psychiatric epidemiologists with the rise of large data sets. Prediction modeling may provide valuable information about the nature of risk factors and eventually aid clinical diagnostics and prognostics. Thus, the studies included in this thesis seek to examine the etiology, associations, and prediction approaches of psychiatric disorders and adverse behaviors.

Study I examined the individual and familial association between type 1 diabetes (T1D) and eating disorder diagnoses. We used national health care records from Denmark (n = 1,825,920) and Sweden (n = 2,517,277) to calculate the association within individuals, full siblings, half siblings, full cousins, and half cousins. Individuals with T1D had twice the hazard rate ratio of being diagnosed with an eating disorder compared to the general population. There was conflicting evidence for the risk of an eating disorder in full siblings of T1D patients. However, there was no evidence to support a further familial relationship between the two conditions.

Study II aimed to illuminate the nature of the correlates for BPD across time, sex, and for their full siblings. We examined 87 variables across psychiatric disorders, somatic illnesses, trauma, and adverse behaviors (such as self-harm). In a sample of 1,969,839 Swedes with 12,175 individuals diagnosed with BPD, we found that BPD was associated with nearly all of the examined variables. The associations were largely consistent across time and between the sexes. Finally, we found that having a sibling diagnosed with BPD was associated with psychiatric disorders, trauma, and adverse behaviors but not somatic illnesses.

Study III created a prediction model that could predict who would have high or low psychiatric symptoms at age 15 based on data from parental reports and national health care registers collected at age 9 or 12. Additionally, we compared multiple types of machine learning algorithms to assess predictive performance. The sample included 7,638 twins from the Child and Adolescent Twin Study in Sweden (CATSS). Our model was able to predict the outcome with reasonable performance but is not suitable for use in clinics. Each model performed similarly indicating that researchers with similar data and research questions do not need to forgo standard logistic regression.

Study IV aimed to determine if an individual will exhibit suicidal behaviour (self-harm or suicidal thoughts), aggressive behaviour, both, or neither before adulthood with prediction modeling. Through variable importance scores we examined the usefulness of genetic variables within the model. A total of 5,974 participants from CATSS and 2,702 participants from the Netherlands Twin Register (NTR) were included in the study. The model had adequate performance in both the CATSS and NTR datasets for all classes except for the suicidal behaviors class in the NTR, which did not perform better than chance. The included genetic data had higher variable importance scores than questionnaire data completed at age 9 or 12, indicating that genetic biomarkers can be useful when combined with other data types

In conclusion, the development of psychiatric disorders and symptoms are associated with many factors across somatic illnesses, other psychiatric disorders, trauma, and harmful behaviors. The results of this thesis demonstrates the limitations of prediction modeling in psychiatric clinics but highlights their use in research and on the path forward towards personalized medicine.

LIST OF SCIENTIFIC PAPERS

I. **Tate AE**, Liu S, Zhang R, Yilmaz Z, Larsen JT, Petersen LV, Bulik CM, Svensson AM, Gudbjörnsdottir S, Larsson H, Butwicka A. Association and Familial Coaggregation of Type 1 Diabetes and Eating Disorders: A Register-Based Cohort Study in Denmark and Sweden. Diabetes Care. 2021 May 1;44(5):1143-50.

II. **Tate AE**, Sahlin H, Liu S, Yi L, Lundström S, Larsson H, Lichtenstein P, Kuja-Halkola R. Borderline Personality Disorder: associations with psychiatric disorders, somatic illnesses, trauma, and adverse behaviors [Manuscript]

III. **Tate AE**, McCabe RC, Larsson H, Lundström S, Lichtenstein P, Kuja-Halkola R. Predicting mental health problems in adolescence using machine learning techniques. PloS one. 2020 Apr 6;15(4):e0230389.

IV. **Tate AE**, Akingbuwa WA, Karlsson R, Hottenga JJ, Pool R, Boman M, Larsson H, Lundström S, Lichtenstein P, Middeldorp C, Bartles M, Kuja-Halkola R. A Genetically Informed Prediction Model for Suicidal and Aggressive Behaviour in Teens [Manuscript]

CONTENTS

LIST OF ABBREVIATIONS

ADHD	Attention-deficit hyperactive disorder
AED	Any eating disorder
AN	Anorexia nervosa
A-TAC	Autism tics and other comorbidities
AUC	Area under the precision recall curve
BBPD	Brother diagnosed with borderline personality disorder
BMI	Body mass index
BPD	Borderline personality disorder
CATSS	The Child and Adolescent Twin Study in Sweden
CBCL	Child and Behavioral Checklist
CDR	Cause of death register
DSM	Diagnostic Statistical Manual
FES	Family environment scale
GWAS	Genome wide association studies
HR	Hazard ratio
ICD	International Classification of Diseases
LISA	The Longitudinal Integration Database for Health Insurance and Labor Market Studies
MBR	The Maternal Birth Register
MDD	Major depressive disorder
MGR	The Multi-Generation Register
NCR	The National Crime Register
NPR	The National Patient Register
NTR	The Netherlands Twin Register
OED	Other eating disorder besides anorexia nervosa
PCRI	The Parent Child Relationship Inventory
PDR	The Prescribed Drug Register
PGS	Polygenic risk score
PTSD	Post-traumatic stress disorder
ROC	Receiver operating curve

RPQ	The Reactive and Proactive Questionnaire
SBPD	Sister diagnosed with borderline personality disorder
SCM	Statin child monitoring
SDQ	The Strengths and Difficulties Questionnaire
SNP	Single-nucleotide polymorphisms
STI	Sexually transmitted infections
T1D	Type 1 diabetes
YSR	The Youth Self Report

1 INTRODUCTION

Psychiatric disorders are syndromes arising from psychological, biological, or developmental factors that substantially affect a person's behavior, cognition, or emotions [1]. Broadly, psychiatric disorders can be separated into two domains: internalizing and externalizing disorders. Internalizing disorders are characterized by distress emotions such as anxiety or depression, while externalizing disorders are marked by uncontrolled behavior that is typically aggressive, delinquent, or hyperactive in nature [2, 3].

The Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD) are the two main clinical handbooks for diagnosing psychiatric disorders. Both manuals consider psychiatric disorders to be binary, i.e., a person either has the psychiatric disorder or does not. However, there are subtle differences between the two in certain disorder names or symptom criteria. In addition, the DSM is primarily used in the United States, whereas the ICD is used internationally and is also used to diagnose somatic illnesses or conditions.

Psychiatric disorders are among the most prevalent health conditions. An estimated 20% of adults and 17% of adolescents meet the diagnostic criteria for a psychiatric disorder each year in the United States [4]. Although the incidence, social consequence, and mortality of these disorders are high, they are taken less seriously and are more stigmatized than physical illnesses of the same societal burden [5, 6]. Thus, the prevention and early detection of psychiatric disorders are important to reduce burdens at an economic, societal, and personal level.

Early detection can be achieved by first identifying the risk factors associated with the development of psychiatric disorders. Next, the risk factors can be used in prediction models which could help identify those in need of clinical follow up or future intervention cheaply and efficiently. Prediction models, often synonymous with machine learning models, are algorithms that predict outcomes or future events based on patterns in existing data. Given

that early detection and evidence-based treatments can mitigate or even prevent the development of psychiatric disorders, the development of models that cohesively apply all known disease markers is sorely needed.

Thus, although merely identifying risk factors associated with psychiatric disorders cannot give insight to the causal mechanisms, it advances our understanding and could contribute to the clinical diagnostic process. This thesis seeks to understand the associations and prediction approaches of severe psychiatric disorders and behaviors.

2 LITERATURE REVIEW

Although all psychiatric disorders cause impairment in patients' daily functioning, some disorders confer exceptional increases to mortality and complications throughout the lifespan. In particular, eating disorders and borderline personality disorder (BPD) are associated with profound hardships across many domains. In conjunction with psychiatric disorders, adverse behaviors such as aggressive behavior and self-harm signify disruptions on a societal and personal level. Given the burden associated with eating disorders, BPD, and adverse behaviors it is of special interest to better understand them through examining their associated risk factors and outcomes. Moreover, the recent interest in advancing personalized medicine in psychiatry through prediction modeling provides hope for better target treatment and intervention

2.1 PSYCHIATRIC DISORDERS

2.1.1 Eating Disorders

Eating disorders, e.g., anorexia nervosa, bulimia nervosa, and binge eating disorder, represent a cluster of psychiatric disorders distinguished by dysfunctional behaviors surrounding food that significantly damage patients' physical health and functioning. The lifetime global prevalence of eating disorders is estimated to be 8.4% for women and 2.2% for men [7]. Although often thought of as a homogenous illness, the disorders that fall within this category have diverse symptom presentation.

According to the DSM-5 [1], the core features of anorexia nervosa are an intense fear of gaining weight, disturbance of body perception, and a restriction of food intake leading to a low body mass index (BMI). Similarly, individuals with bulimia nervosa have a fear of weight gain and body perception disturbances. However, bulimia nervosa is characterized by reoccurring episodes of binge-eating and compensatory behaviors, e.g., self-inducted vomiting, to avoid weight gain. Binge-eating is defined as a loss of control over eating and consuming more than what most individuals would in the same setting. Patients with binge-eating disorder have reoccurring episodes of binge-eating without compensatory behaviors.

Although eating disorders can develop at any age, the average age of onset for anorexia nervosa and bulimia nervosa is in the mid- to late teens, whereas binge eating disorder is typically adult onset [8, 9]. The relatively young age of onset is sobering in the context of the complications that can arise. The standardized mortality ratio of 5 for anorexia nervosa and 1.7 for bulimia nervosa are among the highest of any psychiatric disorder [10]. That said, the clinical recovery rates are promising. Nearly 70% of patients recover after 10 years, and early intervention can improve these rates [11].

2.1.2 Borderline Personality Disorder

BPD, also called emotional unstable personality disorder in the ICD, is a severe and often misunderstood diagnosis, which affects 1.7% of the global adult population [12]. The core features of this diagnosis affect many facets of life: unstable interpersonal relationships, feelings of emptiness, volatile mood swings, reoccurring self-harm and suicidal ideation, and a deep fear of abandonment [1]. Perhaps the most prominent symptom is emotional dysregulation, an inability to regulate emotions combined with high emotional intensity, which results in impulsive and maladaptive behavior to escape negative emotions [13]. The actions resulting from emotional dysregulation often negatively impact these patients' lives.

Patients with BPD had lower global functioning across different raters, i.e., evaluators, compared to patients with major depressive disorder (MDD) or other personality disorders [14]. There is an increased risk of early mortality and completed suicide; the standardized mortality ratio has been estimated to be between 3.5 - 4.8[15]. Additionally, a study by Zanarini, et al., found that 9% of 290 patients died within 16 years, with half of those deaths due to suicide [16]. Compounding the severity of this illness, there is a social and clinical stigma for receiving a BPD diagnosis, even among clinicians [17]. Although treatments exist that are specifically aimed towards BPD and emotional regulation, e.g., dialectical behavior therapy, these targeted interventions have not proven better than treatment as usual in BPD diagnosis [18]. That said, Zanarini, et al., found that 60% of patients reached remission after 16 years of follow up [16].

2.2 NEGATIVE OUTCOMES

Psychiatric disorders are associated with worse life course outcomes such as low educational or occupational attainment, cognitive impairment, younger age of childbirth, and relationship instability [12, 19-22]. Additionally, individuals with psychiatric disorders are at a higher risk of crime victimization and other traumatic events [23-25]. Broadly, the extent of negative life course outcomes is correlated with an early age of onset, comorbid psychiatric disorders, and disease severity [26, 27]. To highlight the hardship associated with BPD, it is the only personality disorder for which an individual can receive full disability benefits in the United States [28]. Self-harm, suicide, and criminality are perhaps the most severe outcomes.

2.2.1 Suicide and Intentional Self-harm

2.2.1.1 Self-harm

Self-harm is defined as intentional self-harm with non-suicidal intent, e.g., cutting or burning, and is closely tied to certain psychiatric disorders, such as BPD. Many of the studies on self-harm do not distinguish between self-harm with or without suicidal intent, which makes study comparisons difficult [29].

The lifetime global prevalence of self-harm is estimated to be 18% and rates tending to peak during adolescence [30]. However, the majority of instances of self-harm are not treated by a medical professional, which can make estimates difficult to obtain from national health care records data [31]. Even so, severe presentations are still captured; many individuals who die from suicide have a documented history of self-harm, with 15% treated in emergency care for self-harm injuries before their deaths [32]. While death from suicide is more common in males, females tend to have higher rates of self-harm [33]. Unfortunately, treatment for self-harm is largely ineffective [34], meaning better interventions are sorely needed.

As self-harm is a core feature of BPD, it follows that BPD has one of the most prominent self-harm rates of any psychiatric disorder. Previous studies found that 90 - 95% of patients have reported self-harming behaviors while more than 75% have attempted suicide [35]. Moreover,

30-40% of patients with an eating disorder have been observed to have a history of self-harm [36], and some might argue that the behaviors associated with eating disorders are forms of self-harm in and of themselves.

2.3 SUICIDE

When talking about suicide or early mortality in epidemiology, the focus is on the numbers and the bigger picture of the societal outcomes; however each death is preventable and represents a person's family member, friend, and neighbor. Suicide has been proposed to be a spectrum of stages, beginning with suicidal ideation, i.e., thoughts of ending one's life, and progressing to the presence of plan for a method of death or increased feelings of hopelessness. Finally, an individual acts on the desire to end their life [37]. However, not everyone with suicidal ideation will attempt suicide.

The integrated motivational-volitional model of suicidal behavior has been proposed to explain the transition between the stages [38]. Insight is needed into specific factors that move an individual from passive thoughts of suicide to active planning behavior. Individuals with specific psychiatric disorders are more at risk than others for death by suicide [37]. Disorders with impulsive-aggressive traits such as attention-deficit hyperactive disorder (ADHD) and BPD increase one's risk of suicide attempts and deaths. In a clinical sample of patients with BPD studied over 10 years, nearly half of all deaths were from suicide [12]. Additionally, one in five deaths of patients with anorexia nervosa is by suicide [10]. One study found that 7.4% of patients with anorexia nervosa and over 25% of patients with bulimia nervosa have attempted suicide [39].

2.3.1 Criminality and Aggression

Broadly, crime can be separated into violent crime, e.g., murder or sexual assault, and nonviolent crime, e.g., theft or property damage. By definition, criminality, especially when aggressive in nature, is strongly associated with externalizing and impulsive disorders.

However, literature suggests a broad association between psychiatric disorders and criminality. In a longitudinal study, nearly half of all offenders had a documented history of any psychiatric disorder in childhood, the most common being anxiety disorders, MDD, and oppositional defiant disorder [40].

2.3.1.1 Violent crime

In a sibling comparison study [41], individuals with personality disorders, including antisocial personality disorder and BPD, had four times the risk of committing a violent offense, while individuals with depression or anxiety had a twofold increase. Crick and Dodge suggested a theory that divides violent acts into two categories: proactive aggression, i.e., premeditated actions, and reactive, i.e., impulsive, provoked behaviors [42]. Proactive aggression is associated with a family history of substance use disorder, poor peer relationships, hyper-activity, and a blunted affect [43]. Moreover, proactive aggression is correlated with a lack of empathy, also termed callous unemotional traits. Callous unemotional traits are fairly stable and sometimes already exhibited by preschool-aged children [44]. Adolescents with callous unemotional traits were found to initiate more fights at age 7 [43].

Reactive aggression is associated first and foremost with impulsivity and emotional dysregulation [45]. Adolescents who exhibit reactive aggression frequently have childhood symptoms of executive dysfunction and paranoid ideation which can affect their social functioning [42]. Moreover, adolescents with instances of reactive aggression have increased symptoms of personality disorders, such as antisocial personality disorder and BPD [46].

2.3.1.2 Nonviolent crime

Considerably less research has been done on nonviolent crime compared to violent crime within psychiatric research. However, research supports many overlapping pathways between nonviolent and violent crime, such as harsh punishment and emotional dysregulation [47]. However, when both disorders are placed into context, nonviolent crime has been more closely

associated with peer delinquency in adolescence in the presence of poor parental relationship [47, 48]. In other words, for adolescents without strong relationships with their parental figures, friendships can take the place of familial bonds. When faced with the opportunity to increase group cohesion by rule breaking, these individuals are more likely to commit a nonviolent offense [49]. Furthermore, reduced parental monitoring could enable more opportunities to commit crimes.

2.4 ETIOLOGY

In an effort to mitigate the hardships associated with BPD, eating disorders, and adverse behaviors it is important to recognize and understand their early precursors. Literature has reported risk factors for developing psychiatric disorders that span interwoven heritable and environmental components.

2.4.1 Heritability and Genetic Architecture of Psychiatric Illnesses

All psychiatric illnesses are, in part, heritable [50]. Heritability is defined as the proportion of variation in the population of a trait or illnesses that is due to genetic differences [51]. In other words, heritability is not the percentage of the trait itself that is caused by genetic factors, but rather the percentage of the differences between individuals in a population. Notably, the heritability rates of psychiatric disorders are higher than many other disorders that are frequently seen as heritable, such as breast cancers and Parkinson's disease [52]. Thus, it is impossible to talk about the development of psychiatric diseases without discussing genetics.

Genome wide association studies (GWAS) are a common way to study the genetic underpinnings of disorders and traits. GWAS compare controls to those with the target illness or trait by identifying single-nucleotide polymorphisms (SNP) or small nucleotides, i.e., cytosine, guanine, thymine, and adenine, at selected locations throughout the genome. Typically, GWAS do not have hypotheses and require a stringent genome-wide p-value threshold to correct for multiple testing. It is clear from GWAS that most complex traits and

diseases are polygenic, i.e., there is no single gene that causes or leads to a trait or disease; rather, there are many SNPs with small effects that aggregate to create an effect [50].

The results of GWAS can be used to calculate polygenic scores (PGS) in a target sample, which sums up risk alleles across the genome weighted by their corresponding effect sizes [53]. Although, PGS can serve as a risk prediction tool for disease or trait development, these scores can only provide a continuous risk percentage of development for traits or illness, not definitively predict if an individual will indeed develop the trait or disorder. However, as many psychologists have come to see most psychiatric illness as a continuum of symptoms rather than a binary diagnosis, perhaps this mirrors the genetic contribution to the underlying structure of these illnesses [54].

2.4.2 Environmental Factors

Disentangling environmental factors from heritable causes in the development of psychiatric disorders can be challenging, but is typically done through twin and family research (discussed at length in 4.2.1). However, factors such as childhood neighborhood quality, peer and familial relationships, and trauma have all been found to impact psychiatric health.

Living in a lower socioeconomic status neighborhood has been associated with an increase in internalizing problems and ADHD [55, 56]. Neighborhood quality has been shown to affect mental health through peer groups, social norms, and available institutional resources [57]. However, it is also possible the relationship between living in a deprived neighborhood and mental illness is partially confounded through heritable parental traits, similar to findings for violent behavior and substance misuse [58].

2.4.2.1 Peer relationships and social contagion

As is the case with criminality, poor peer relationships and bullying can influence symptoms of psychiatric disorders. Bully victimization in childhood is associated with adult psychiatric disorders including anxiety disorders, depressive disorders, and suicidality [59]. On the other

hand, bullying behavior is also associated with externalizing disorders and the later development of antisocial personality disorder [60]. This effect appears to be bidirectional, as children with MDD, ADHD, conduct disorder, substance use disorders, and anxiety disorders tend to report more peer conflict and greater social difficulties [61].

Social contagion, i.e., mutual peer influence, is common with suicide and self-harm as well as restrictive eating disorders [62]. Thus, a friend receiving positive social feedback for modeling eating disorder or self-harming behavior could be a major contributing factor toward bringing an individual to self-harm or to exhibit disordered eating behavior.

2.4.2.2 Childhood trauma and comorbid post-traumatic stress disorder

Childhood abuse and/or neglect has been associated with a later diagnosis of psychiatric disorders. Breaking down childhood trauma by type has primarily yielded non-specific effects on the development of psychiatric symptoms, as individuals often have multiple types of trauma [63, 64]. That said, many psychiatric disorders have been associated with general childhood trauma, e.g., chronic depression, anxiety disorders, and eating disorders [25]. For example, up to 90% of patients with BPD are estimated to have experienced some form of trauma [65]. However, post-traumatic stress disorder (PTSD) is the most defining psychiatric disorder to develop following a traumatic event [66-68].

To highlight the extent of the connection between trauma, BPD and PTSD, some researchers and clinicians have argued for a subtype of PTSD called disorders of extreme stress not otherwise specified, or complex PTSD [69, 70]. This proposed subtype bears a striking resemblance to a BPD symptom profile, including emotional dysregulation, volatile relationships, and identity disturbances [71]. While complex PTSD was ultimately not included in the DSM-5 or ICD-11, the observation of a distinct PTSD symptom profile closely matching that of BPD by clinicians specializing in PTSD highlights the deeply tied association.

2.5 COMORBIDITIES

2.5.1 Psychiatric Comorbidity

Comorbidity for psychiatric illnesses is pervasive. One outpatient psychiatric clinic found that over half of all patients with any psychiatric illness fit the criteria of at least two or more psychiatric illnesses [72]. This study supports the so-called "rule of 50%", meaning around 50% of patients with a psychiatric disorder meet the full criteria for a second, half of those patients meet the criteria for a third diagnosis, and so on [73]. Moreover, it is not uncommon for new symptoms or disorders to develop after the initial diagnosis, as the absolute risk for developing another disorder is as high as 40% [74]. Even if patients do not meet the full criteria for another disorder, multiple symptoms that are outside of their primary diagnosis may be present which can severely affect a patient's functioning.

2.5.1.1 Mechanisms behind psychiatric comorbidities

The mechanisms underlying the high rates of comorbidities within psychiatric disorders likely stem from a combination of factors. For example, the dichotomization of continuous traits may result in a poor or unspecific classification. Moreover, a shared genetic architecture may underlie all psychiatric disorders. Substantial research has shown that most psychiatric disorders and symptoms are primarily extreme ends of right-skewed distributed traits, however diagnostic tools still treat these illnesses as strictly categorical, distinct illnesses [75].

The debate between categorical versus dimensional approach is not an issue unique to psychiatric disorders, physical illnesses such as hypertension face similar issues [76]. However, the DSM and ICD still contain a binary model of disease presence. This is due to a number of reasons: tradition, a shorthand for describing a patient's symptom profile and/or first line treatment course [76]. Additionally, pressure for binary diagnosis comes from external sources, e.g., insurance companies or public health agencies, which require a binary diagnosis in order to determine coverage for a particular patient, treatment round, or public policy decisions.

The call for a standardized guideline for an evidence-based, dimensional approach towards psychiatric disorders has resulted in the Research Domain Criteria [54]. This manual focuses on symptomology and the basic biological and behavioral components. Furthermore, it seeks to reduce the fluctuations in disease categorization and remove biases based on artificial cut-offs [54].

2.5.1.2 General psychopathology factor

The general psychopathology factor, or p factor, was coined in the 2010s to describe the general, underlying dimension behind psychiatric disorders [77]. It is meant to mimic the general intelligence factor, or g factor, that underlies performance on intelligence tests. Although intelligence tests measure intelligence scores across several domains, the underlying g factor explains the overall correlation between the scores, and insinuates a similar genetic etiology [78, 79]. Factor analysis, a model that seeks to find the smallest number of factors that account for the correlation between variables, was found to perform similarly on psychiatric symptom subscales compared to intelligence test subscales: One emerging factor explained most of the correlation between the scores [77]. In addition to common factor analysis, evidence from genetic and family studies also support the p factor [80-82]. As all psychiatric disorders are correlated to some extent researchers should keep the general p in mind when attempting to examine specific comorbidities. The relationship between specific comorbidities may be solely capturing the effect of the general p factor, for example the correlation of all neurodevelopmental disorders is not limited to ADHD and autism spectrum disorders [81].

2.5.2 Somatic Comorbidities

Psychiatric disorders are strongly associated with somatic comorbidities, i.e., physical illnesses, be it through a shared underlying genetic architecture or behavioral influences [83]. A large Danish study found that psychiatric disorders were associated with an increased risk of nearly all somatic comorbidities to varying degrees [84]. For example, chronic illnesses, such

as asthma, appear to have a bidirectional relationship with psychiatric disorders [85, 86]. Similarly, cardiovascular disease has been associated with the majority of psychiatric disorders including BPD [87].

As disordered eating behaviors directly affect the body, somatic complications are common. Individuals with binge eating disorder are at a higher risk for obesity, and the vomiting associated with purging behavior often damages tooth enamel leading to poor dental health. Moreover, eating disorders as a whole are associated with urogenital, hematological, and musculoskeletal disorders [84]. Finally, eating disorders appear to have a bidirectional relationship to autoimmune disorders in women [88].

2.5.2.1 Type 1 diabetes

Type 1 diabetes mellitus (T1D) is an autoimmune disorder that results from damage to pancreatic B-cells, leading to chronic insulin deficiency and hyperglycemia. An individual can develop the disease at any time, but diagnosis peaks in childhood and adolescence. T1D accounts for 5 – 10% of diabetes cases and has been found to be increasing in prevalence worldwide [89]. There is currently no cure, and disease management involves careful monitoring of blood sugar and food intake as well as insulin injections. T1D has been associated with psychiatric disorders and suicidality in adolescence [90]. Specifically, eating disorders have also been found to be strongly associated with T1D and other autoimmune disorders [90, 91]. Type 2 diabetes is characterized by slower onset of insulin deficiency and hyperglycemia. Typically, onset occurs in adulthood and is frequently associated with obesity and dietary factors [92].

2.6 PREDICTION MODELING IN MENTAL HEALTH

With the rise of large epidemiological data sets involving health care data, psychiatric researchers have become increasingly interested in using prediction modeling to assist clinical assessment and treatment decisions [93]. Prediction modeling is often synonymous with

machine learning algorithms (defined in section 4.2.1.1), and has generated considerable interest from industry and academia in the age of big data, i.e., large datasets. Despite its relatively futuristic name, machine learning has been used since the 1950s and includes techniques commonly used by researchers, such as logistic regression.

Prediction modeling has been touted as a path toward improving diagnostics, prognosis, and treatment response in clinical settings. Hopefully, it will ultimately lead to the crowning jewel in modern health care: precision medicine. Currently, the path towards the correct psychiatric treatment is arduous. It typically takes multiple sessions of interviews to receive a clinical diagnosis and medication is prescribed via trial-and-error, with each prescription possibly requiring weeks to take effect, Advancements in precision medicine would mean an individual could quickly receive a likely diagnosis based on data from biomarkers, genetics, and short clinical interviews. Then, a suggested course of medication and psychotherapy with individualized terms can be recommended. The suggestions can guide clinicians in making their final decision and can allow them to utilize the full scope of available data.

As of 2022, prediction modeling in psychiatry is in its infancy; to the author's knowledge only a handful studies are ready for use in clinical settings in certain specific samples. Suicide seems to be the most common outcome by far, as shown in [94-97]. Predictors often include variables derived from clinical reports, questionnaires, electronic health records, and biological markers. In combination with the large population-representative samples provided by national health care registers, prediction models could become a boon for general population screening. As teachers and parents may miss signs of potential developing psychiatric illnesses, prediction models may help to quickly and cheaply identify individuals in need of follow up or early intervention programs.

2.6.1 Prognostic Models

Prognostic prediction models examine functional outcomes such as psychosis, relapses, or suicide [98]. According to a recent systematic review, prognostic models were the most common type of study and were the only replicated prediction models [99]. However, current models are not suitable for clinical use due to low performance metrics [100, 101].

2.6.1.1 Suicide

Death from suicide is the perhaps the most severe, preventable outcome in psychiatry, so it follows that suicide is the focus of many psychiatric prediction models. The studies that examine the spectrum of suicide stages primarily feature clinical or military samples [100, 102].

2.6.2 Diagnostic Models

A systematic review found that the most common psychiatric diagnostic models were for MDD, bipolar disorder, anxiety disorders, PTSD, and schizophrenia and other psychotic disorders. The studies included within the review consisted of small sample sizes and none used an external validation sample, indicating that clinical use is still not yet feasible [103]. A more recent study was able to create a model that distinguished unipolar depression from bipolar disorder using neuroimaging data with reasonable accuracy in an external validation sample [104].

2.6.3 Treatment Response Models

Devising the correct course of pharmacologic treatment for psychiatric disorders is often difficult. The context for patients' individualized response to medication is unknown and it can take many iterations before a best course is decided, as is the case with ADHD medication. Between two examples of front line treatments, methylphenidate and amphetamines, patients' responses are mixed between better responses to one treatment or a combination, but around 15% did not respond to either [105]. Thus, one of the largest promises of prediction modeling is removing this guess work. One such study with ADHD medication found promising results

in a model that used clinical interviews and functional magnetic resonance imaging data in a small sample size [106]. Additional progress has also been made in regards to treatment responses in other disorders, such as MDD [107]. While these results must be replicated in larger sample sizes, the proof of concept is a promising step towards personalized medicine.

2.7 RATIONALE FOR PRESENT THESIS

In summation, psychiatric disorders have far reaching consequences throughout an individual's life, which are especially compounded in the case of severe psychiatric disorders. Additionally, prediction models offer exciting new potential for psychiatric researchers and clinicians.

2.7.1 Study I

2.7.1.1 The association of type 1 diabetes and eating disorders.

Eating disorders are associated with T1D [90, 91]. The comorbidity of eating disorders and T1D creates serious health risks to patients including premature death in the face of an already shortened lifespan [108-110]. This is especially true in the context of purging subtypes [111]. As insulin manipulation is associated with weight fluctuations, under-dosing insulin represents a unique method of weight control or compensatory behavior for diabetes patients [112]. A longitudinal study found that 30% of women with T1D reported under-dosing insulin, and the behavior was associated with higher eating disorder symptoms and mortality [110]. To further compound these complications, treatment is often a complex balance of managing both diseases, e.g., glucose control during the refeeding stage of severe anorexia nervosa [113, 114]. Thus, while T1D may correlate with many psychiatric disorders, the comorbidity with eating disorders represents a special, pressing health concern that requires special attention from both researchers and physicians. However, comprehensive estimates of this association have not yet been presented from an international sample broken down by eating disorder subtypes.

2.7.1.2 The etiology of comorbid type 1 diabetes and eating disorders

The etiology of the comorbidity of T1D and eating disorders is unclear. There are conflicting studies regarding a shared genetic liability. Both disorders have been found to be heritable [115,

116]. A Swedish study that examined the comorbidity of T1D and psychiatric disorders found a non-statistically significant association, although this study only examined full siblings and did not examine specific eating disorder subtypes. Moreover, the first GWAS for anorexia nervosa identified a location of the genome that has been associated with T1D and other autoimmune disorders [117]. However, this did not hold true in a more recent GWAS [118].

Alternatively (or in conjunction with genetic factors), the etiology of this comorbidity could be driven by the consequences of having T1D itself, e.g., increased food monitoring and stress. Children with chronic illnesses, such as T1D, have an increased likelihood of developing a psychiatric disorder [119]. However, a bidirectional relationship has been reported between eating disorders and autoimmune disorders including T1D [88]. This indicates that the stress and behavior changes with T1D itself cannot be the only driver of this association. Thus, the etiology behind this comorbidity must be clarified given both the severity of the outcomes as well as the conflicting literature.

2.7.2 Study II

2.7.2.1 Associations between borderline personality disorders and psychiatric disorders, somatic illnesses, and adverse behavior

Borderline personality disorder and psychiatric comorbidities

As BPD is a severe psychiatric disorder, it follows that psychiatric comorbidities are the rule rather than the exception. Illustrating this, one Swedish study found that nearly all individuals diagnosed with BPD in national health registers were also diagnosed with another psychiatric disorder [120]. Most commonly, BPD has been associated with anxiety disorders, bipolar disorders, impulsive disorders, MDD, and PTSD [12]. In short, receiving a BPD diagnosis appears to be associated with an increased vulnerability for comorbidities. However, detailed epidemiological studies into the BPD diagnosis are lacking. Moreover, given that all psychiatric disorders are correlated to some extent, it is unclear which disorders have

exceptionally high estimates in a representative population sample, and thus should be the focus of future intervention strategies.

Borderline personality disorder and somatic comorbidities

BPD patients frequent health care clinics at a higher rate than those with other psychiatric diagnoses [121]. A BPD diagnosis has been linked to sexually transmitted infections (STIs), obesity, diabetes, hypertension and chronic pain [122, 123]. Individuals with BPD were also found to have twice the prevalence of metabolic disorders, leading to an increased risk of type 2 diabetes [124]. Moreover, epilepsy is commonly associated with this disorder, certain personality changes as a result of seizures can strongly resemble the symptoms of BPD [125]. Several relevant somatic illnesses may have been previously understudied in smaller BPD studies, one such example is infertility. Although studies have linked BPD to polycystic ovary syndrome and obesity, both of which both inhibit fertility, little research exists on the specific link between infertility and a BPD diagnosis [126, 127]. Adding to the complication of studying rare somatic conditions, individuals with BPD often report greater illness severity than their medical records, which indicates the need for objective measurement [128]. Thus, objective, large scales studies are needed to illuminate the association between receiving a BPD diagnosis and somatic illnesses.

Borderline personality disorders, adverse behaviors, and trauma

BPD is closely associated with adverse behaviors such as criminality and self-harm. Estimates suggest that 20-50% of United States inmates of both sexes meet the criteria for BPD [129]. Research has linked violent crime, specifically domestic violence, to this patient population [129, 130], although little is known about the estimates and nature of nonviolent crime committed by individuals diagnosed with BPD.

BPD has one of the most prominent self-harm rates of any psychiatric disorder. Self-harm is a core feature of BPD; 90 – 95% of patients have reported self-harming behaviors and more than

75% have attempted suicide [35]. Precise estimates highlighting the magnitude of this association have not yet been presented in a population sample.

As previously stated, trauma, BPD, and PTSD are strongly correlated. There is inconclusive evidence for the association between BPD by trauma type, but sexual assault seems to be the most prevalent [63, 64, 131]. However, certain trauma types have not been examined in individuals with BPD, such as the death of a parent or sibling. Additionally, it is unclear the extent to which trauma may be directional [132].

Moreover, similar to somatic reports, capturing objective measures of trauma would prevent biases that may arise from self-reports [133]. Thus, it is of interest to examine the nature of self-harm, criminality, and specific trauma types identifiable in national register data.

Directionality, sex differences, and etiological associations

It is of interest to delve into the nature of the aforementioned associations. In particular, the directionality of the diagnoses or events could provide information on the diagnostic pathways toward a BPD diagnosis, and pertinent areas for clinical vigilance.

There are documented sex differences within BPD [46, 134, 135]. Evidence points to a 3:1 ratio of females to males who are diagnosed, although epidemiological studies suggest equal prevalence between the sexes [134]. With the likely diagnostic bias present within clinics, males are underrepresented in clinical studies. Thus, national register studies provide a unique opportunity to examine the sex differences within the associations. If a diagnostic bias was indeed present in the national registers, it is likely that males would need more severe symptom presentation in order to receive a diagnosis. Thus, we would expect to see higher estimates for the studied variables in males compared to females.

Further, we hypothesize that there is no true difference in the etiology of BPD symptoms between males and females, based on what is known on the genetics behind mood and psychiatric disorders that predominately affect females, e.g., anorexia nervosa [118, 136].

Additionally, a sex linked disorder would indicate a greater prevalence in males than females. Therefore, examining individuals with a brother or sister with BPD would provide additional support for a diagnostic bias between the sexes. If individuals with brothers diagnosed with BPD had higher estimates than individuals with sisters, it would provide evidence of a more severe phenotype and liability for the development of said associations.

2.7.3 Study III

With the considerable interest around machine learning and prediction modeling in psychiatry, it is of interest to examine the best methods and approaches for psychiatrists who may not be trained statisticians. A wide range of complexity exists within machine learning techniques, and it is unclear if researchers should forgo standard techniques in favor of more complex methods. Although it has been previously theorized that no one model performs better than another on average, this has not been applied within a psychiatric setting. Thus, the aim of Study III is to determine to what extent performances of varying machine learning techniques differ by creating a prediction model that can determine who will have present levels of psychiatric symptoms at age 15.

2.7.4 Study IV

Aggressive behavior and suicidal behaviors, e.g., self-harm and suicidal ideation, cause significant stress to individuals and their loved ones. There is evidence supporting an intertwined connection between suicidal behaviors and violent crime [137, 138]. While suicide has been the focus of many prediction models studies, few have examined self-harming behaviors in the context of aggression [139]. Moreover, these behaviors share many overlapping risk factors, which may indicate that a combined model would represent a more streamlined approach towards prognosis [140-144]. Thus, it is of interest to build a prediction model that can distinguish who will exhibit suicidal behaviors, aggressive behaviors, both, or neither by age 18.

Additionally, there appears to be a genetic and neurobiological basis for the link between impulsive intentional self-harm and aggressive behavior [145]. With this in mind, known PGS of psychiatric disorders may help further uncover the factors that drive these impulsive-aggressive behaviors and improve prediction techniques [146]. However, as PGS are not yet informative on their own within psychiatric clinical settings it is unclear if they may provide key information to prediction models in combination with other data types.

2.8 PRESENT STUDIES

In summation, prevention is the best method for mitigating psychiatric disorders and adverse behaviors, and understanding the etiology is the first step in doing so. The underlying link between eating disorders and T1D is especially pertinent to understand, given the conflicting evidence for a shared genetic etiology. Moreover, BPD is one of the most challenging disorders to treat and many factors have been implicated in the etiology and life-course outcomes. The reported associations with BPD must be placed into context with each other to determine the most pertinent avenues for clinical interventions and future studies. In tandem, the use of prediction models that utilize the findings of etiological and association studies could help better target the interventions to patients who would benefit the most.

Machine learning models promise insight into clinical and research applications. Psychiatric epidemiologists may raise the question if it is worth forgoing familiar methods, i.e., logistic regression, in order to use more complicated machine learning techniques. Moreover, machine learning techniques can handle intricate relationships between predictors, so even predictors with comparatively weak associations to the outcome in question may be of interest to include. This inquiry is applicable in the case of genetic data, such as PGS, as the scores themselves are not yet clinically relevant. However, the usefulness may be boosted in a model containing other data types [147].

3 RESEARCH AIMS

3.1 OVERARCHING AIM

The overarching aims of this thesis are twofold: 1.) To understand the context for the development psychiatric disorders and related outcomes (Study I and Study II); 2.) Use known risk factors to build prediction models to determine who will develop psychiatric disorders and associated negative outcomes (Study III and Study IV).

3.2 SPECIFIC AIMS

Study I: Determine the extent of the association and familial co-aggregation of T1D and eating disorders

Study II: 1.) Identify the associations between BPD and psychiatric disorders, somatic illnesses, trauma and adverse behaviors, e.g., crime and self-harm. 2.) Examine their directional associations 3.) Understand the sex differences for individuals with BPD and their families.

Study III: Create a model which predicts mental health problems in mid-adolescence; additionally, we aimed to investigate if common machine learning techniques will outperform logistic regression.

Study IV: 1.) Build a genetically informed prediction model to distinguish between self-harm and aggressive behaviours in late adolescence to early adulthood. 2.) Determine the extent to which genetic data in the form of PGS are informative to the model.

4 MATERIALS AND METHODS

4.1 MATERIALS

4.1.1 Data sources

Multiple Swedish national registers were utilized to obtain the data for Studies I and II. Study III used a combination Swedish national register data as well as data from the Child and Adolescent Twin Study in Sweden (CATSS). The data for Study IV came from CATSS as well as the Netherlands Twin Register (NTR).

4.1.1.1 Swedish National Registers

All Swedish national registers are linked through a personal identity number assigned to each individual at birth or immigration. Beginning in 1947, the personal identity number has been routinely used by all governmental agencies is carefully maintained by the National Tax Board [148]. The following registers used in the aforementioned studies:

The Cause of Death Register (CDR) comprises of the date and ICD coded cause of death for all individuals registered and living in Sweden from 1952, not including stillbirths or deaths abroad [149].

The Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA) features data based on income, the use of social services and benefits, as well as neighborhood-specific variables. Starting in 1990, this register has information on all individuals older than 16 registered in Sweden [150].

The Medical Birth Register (MBR) contains detailed information on the maternal perinatal period and birth from 1973 and onwards [151].

The Multi-Generation Register (MGR) provides information of familial relationships, both biological and adoptive, for all individuals born after 1932 who were living in Sweden during 1962 and later [152].

National Crime Register (NCR) consists of criminal convictions for individuals 16 years or older since 1973 [153].

The National Patient Register (NPR) started in 1964 and began collecting information on psychiatric diagnoses from 1972. It contains ICD diagnostic information from all specialist inpatient and ~80% of outpatient visits after December 31, 2000. Before this date only information arising from inpatient care is available. During the follow up time for my studies two ICD revisions were used: the ICD-9 from 1987 until 1996 and the ICD-10 from January 1, 1997 and onwards [154].

Prescribed Drug Register (PDR) has detailed information on all dispensed medication starting July 2005, but does not include medication used during inpatient care [155].

Swediabkids is a diabetes quality register which provides detailed information of an outpatient visit for over 18,000 patients with diabetes in Sweden [156].

Risät and **Stepwise** are national eating disorder quality registers that contain detailed information from specialized treatment centers throughout Sweden [157].

The Total Population Register began in 1968 contains information on familial relationships, birth, death, and migration to and from Sweden [158].

4.1.1.2 Child and Adolescent Twin Study in Sweden

CATSS is an ongoing longitudinal study which contains more than 16,000 twin pairs in Sweden, in which all twins born in Sweden in 1992 or later are eligible to participate [159]. Data collection began in 2004 when the twins were 9 or 12 years old. Information was obtained via interviews with caregivers regarding twins' psychiatric symptoms, behavioral measures, as well as home environment. Follow up self-reported and parental reported questionnaires have been collected at age 15, 18, and 24. Additionally, CATSS contains genotyped data for over 13,000 participants [160]. The response rate for CATSS has decreased with time: the first wave

(age 9 or 12) has a response rate of 80%, the second wave (age 15) has ~55%, and the third wave (age 18) has a response rate of 51% [159].

4.1.1.3 The Netherlands Twin Register

The NTR is an ongoing longitudinal twin study in the Netherlands that started in 1987 and has information on twins, triplets and their families from infancy [161]. Parent and teacher reports are available until age 14, and self-reported data is available from 14 years old onward. Data used for study IV was derived from ages 12, 16, and 18.

4.1.1.4 Danish national registers

Similar to the Swedish NPR, the Danish national registers contain administrative information from individuals connected through a personal identity number assigned at birth. Study I used the Civil Registration System to determine familial relationships [162], the Danish National Patient Register [163] to obtain ICD information for all outpatient doctor visits, and the Psychiatric Central Research Register [164] which contains detailed information on treatment in psychiatric clinics in Denmark.

4.1.2 Outcome Measures

Study I. Eating disorders were measured by the ICD 9 diagnostic code 307B, the ICD-10 diagnostic code F50 from the NPR and the DSM-IV-TR code 307-1 from the quality control registers Riksät and STEPWISE. The Danish analysis used the Psychiatric Central Research Register used the ICD-8 diagnostic codes 306.5, 306.58, and 306.59 as well as ICD-10 diagnostic code F50.8 and F50.9. Both the Danish register and the NPR have been found to have good reliability in psychiatric disorder diagnoses [154, 164].

Study II. Borderline Personality Disorder diagnosis was determined through ICD-10 diagnostic code F60.3 in the NPR, which refers to the diagnosis of emotionally unstable personality disorder. A previous study has shown that the emotionally unstable personality

disorder diagnostic code is analogous to the BPD diagnosis in the DSM, and has good specificity [165, 166].

Study III. Behavioral and psychiatric symptoms was measured by the parent-rated version of the strengths and difficulties questionnaire (SDQ) [167]. The SDQ comprises 25 items and contains information on hyperactivity, conduct problems, internalizing symptoms, social difficulties, and prosocial behavior. The Swedish translation has been validated and was found to have good discrimination between clinical cases and non-cases in a community sample [168]. Additionally, the Swedish version had good internal consistency in both clinical and community sample with a Cronbach's alpha of 0.80. We did not use the prosocial behavior subscale in Study III.

Study IV. Self-harm and aggression were measured through the life history of aggression checklist [169]. This questionnaire features questions related to self-harm, aggression, antisocial behavior, and social consequences on a six point scale: no event, one event, 2-3 events, 4-9 events, 10+ events, and more times than I can count. Self-harm was derived from the questions "Deliberately attempted to injure yourself physically when you were angry or despondent" and "Deliberately attempted to kill yourself when you were angry or despondent". Aggression was measured based on the other questions from the other subscales, such as "Deliberately harmed an animal or person when you were angry". The measure has been found to have suitable internal consistency with a Cronbach's alpha of 0.88 [169].

4.1.3 Predictors

4.1.3.1 Study I

Diagnostic records of **T1D** were calculated using the NPR or Swediabkids (ICD-8 codes 250.00–250.09, ICD-9 codes 250.1–250.9, ICD-10 code E10) within the Swedish sample. Similarly, the Danish sample used ICD-8 codes 250.00–250.09, ICD-10 code E10 from the Danish national patient register.

4.1.3.2 Study II

The predictors for Study II and their sources can be found in tables 4.1.3.2 1-3. The psychiatric and somatic variables were obtained through the NPR, while the trauma and adverse behaviors variables were obtained through the NPR, NCR, and LISA. The neighbourhood deprivation score was originally created by Sariaslan, et. al., (2015) [23]

Table 4.1.3.2 1. ICD codes used to derive psychiatric disorders and subcategories

Name	Subcategories	ICD-9	ICD-10
Affective disorders		300E, 300X, 301B	F34 – F39
Anxiety		300A, 300C	F40, F41, F48
Attention deficit hyperactive disorder		314	F90
Autism spectrum disorder		299A	F84
Bipolar disorders		296A-296E, 296W, 296X	F30, F31
Conduct disorder		312	F91
Depression		296B, 311	F32, F33
Dissociative disorders		298B, 298C, 298W, 298X, 300B, 300F-X, 301W, 306A-X, 307W, 307X, 784G, V40X	F44, F45
Eating Disorders		307B 307F	F50.0, F50.1, F50.2, F50.3, & F50.9
Intellectual disability		307C	F70 - F79
Obsessive compulsive disorder		300D	F42
Personality disorders			F60 (not F603)
	Antisocial personality disorder	301G	F602
	Avoidant personality disorder	301H	F606
	Personality disorder not specified	301I	F609
Post-traumatic stress disorder		308, 309	F431
Psychotic disorders		295A-295E, 295G, 295W, 295X, 295H	F20, F21, F25

	Schizophrenia	295A-295E, 295G, 295W, 295X	F20
	Schizoaffective disorder	F295H	F25
	Schizotypal disorder [a]	295E	F21
Substance use disorder		291A-X, 292A-X, 294A, 303, 304A-X, 305A-X	F10, F11-F19 (not F17)
Tic disorder		307C	F95.0 – F95.2, F59.9

[a] Although considered a personality disorder in the DSM-5, schizotypal disorder is considered a psychotic disorder in the ICD-10

Table 4.1.3.2 2. ICD codes used to derive somatic illnesses and subcategories

Indicators	Subcategories	ICD-9	ICD-10
Asthma		493A-X	J45-J46
Autoimmune disorders [1]		704A, 258B, 136B, 694F, 579A, 555, 710D, 242A, 357.A, 245.C, 287.A, 287.D, 580-582, 446.1, 710.W, 340, 358.A, 694.E, 725, 446.0, 571.F, 696, 390-391, 392, 714.A, 034.1, 710A-C, 446F-G, 556, 709.A, 446.E	G04, L63, G13.1, D68.61, E31.0, M35.2, L12.0, K90.0, M30.1, K50, M33.90, E05.0, G61.0, E06.3, D69.0, D69.3, N00-01, N03, N05, M30.3, M31.7, M35.1, G35, G70.0, L10.0, M35.3, M30.0, K74.3, L40, I00-02, M06, A38.9, M34, M35.0, M32, M31.5, M31.1, E10.9, K51, L80, M31.3
	Intestinal malabsorption	5790	K90
	Psoriasis	683	L40
	Ulcerative colitis	556	K51
Cardiovascular disorders		397X, 394A-B, 394C, 394X, 395A-C, 395X, 396X, 397A-B, 397X, 398A, 398X, 410A-B, 410W-X, 411A-C, 411X, 412X, 413X, 414A-B, 414W, 414X, 420X, 421A, 421X, 422X, 423A-C, 423W, 423X, 424A-D, 424X, 425A-B, 425D-F, 425X, 426A-H, 426W, 426X, 429A-G, 429W, 429X	I05 – I109, I20 – I28, I30 - 152
	Cardiac arrhythmias	426H	I499
	Paroxysmal tachycardia	427X	I471

	Rheumatic heart diseases	401	I109
Diabetes		250	E10, E11
	Type 1		E10
	Type 2		E11
Epilepsy		345J-345N, 345P, 345Q, 345W, 345X	G40
Infertility		628	N97
Obesity		278	E66, Z71.3
Sexually transmitted infection		090A – 099X, 279G, 279J, 279K	A50 – A64, B20, B373
	Chlamydia	0998	A56
	Herpes viral infection	0541	A60
	Venereal warts	0913	A630

[1] Autoimmune ICD codes were obtained from Mataix-Cols D, et al., (2018) [170]

Table 4.1.3.2 3. ICD codes used to derive trauma and adverse behaviors and subcategories

Indicators	Subcategories	Source	Calculation
Accident		NPR	ICD 10: W, X00 – X58 ICD 9: 810 – 949, 99
	Fall	NPR	ICD 10: W0 – W1 ICD 9: 88E
	Object enters eye	NPR	ICD 10: W44 ICD 9: 915E
	Struck by object	NPR	ICD 10: W22 ICD 9: E917
Death of a close family member		CDR	Family connections identified through the MGR
	Death of father	CDR	Family connections identified through the MGR
	Death of mother	CDR	Family connections identified through the MGR
	Death of sibling	CDR	Family connections identified through the MGR
Neighborhood deprivation[1]		LISA	Created from the highest quartile of the neighborhood deprivation score by either averaging the values from ages 5 to 10 or the value at the start of LISA which was used to measure income (year 1990) whichever came last
Poverty		LISA	Created from the lowest quartile of family disposable income by either averaging the values from ages 5 to 10 or the value at the start of LISA which was used to measure

			income (year 1990) whichever came last
Nonviolent crime		NCR	Identified through Sweden-specific criminal codes
	Petty theft	NCR	Identified through Sweden-specific criminal codes
	Fake passports or identification	NCR	Identified through Sweden-specific criminal codes
	Property damage	NCR	Identified through Sweden-specific criminal codes
Self-harm		NPR	ICD 10: X60 – X84, Y10 – Y34 ICD 9: 95, 98
Victim of violent crime requiring medical attention		NPR	ICD 10: X85-Y09 ICD 9: 96
	Physical Assault	NPR	ICD 10:Y04 ICD 9: 960E
	Sexual Assault	NPR	ICD 10: Y05 ICD 9: 961E
	Abuse	NPR	ICD 10: Y07 ICD 9: 967E
Violent crime		NCR	Identified through Sweden-specific criminal codes
	Assault	NCR	Identified through Sweden-specific criminal codes
	Threats of violence	NCR	Identified through Sweden-specific criminal codes
	Committing bodily injury	NCR	Identified through Sweden-specific criminal codes

[1]

4.1.3.3 Study III

The predictors for study III are presented in table 4.1.3.3. The predictors were collected at age 9/12 and consisted of variables obtained from the national registers PDR, MBR, and LISA, as well as questionnaire data from the Autism-Tics, ADHD, and other Comorbidities inventory (A-TAC), Statin Child Monitoring (SCM), and the Sicklist. A-TAC assesses neurodevelopmental problems in childhood and has been found to have good sensitivity and specificity for neurodevelopmental disorders [171, 172]. The SCM measures the level of parental involvement in their child's behavior and activities and had been found to have suitable inter-rater and test retest reliability [43]. Finally, the Sicklist is a basic health questionnaire checklist designed for telephone screening for CATSS data collection.

Table 4.1.3.3. Predictors and their source for Study III

Variable	Source
ADHD symptoms	A-TAC
Attention symptoms	A-TAC
Impulsivity symptoms	A-TAC
Learning difficulty	A-TAC
Autism symptoms	A-TAC
Language difficulty	A-TAC
Peer/social difficulty	A-TAC
Flexibility symptoms	A-TAC
Tics symptoms	A-TAC
Compulsion symptoms	A-TAC
Oppositional defiant disorder symptoms	A-TAC
Conduct disorder symptoms	A-TAC
Caregiver information	Descriptive information
Sex	Descriptive information
Zygosity	Descriptive information
General health	Sicklist
Chronic pain	Sicklist
Depression	Sicklist
Ear tube placed	Sicklist
Ear operation	Sicklist
Eye squint	Sicklist
Stammering	Sicklist
Constipation	Sicklist
Social services involved	Sicklist
Epilepsy	Sicklist
Use of psychiatric medication before interview date	PDR
Mother diagnosed with a psychiatric disorder	MBR & NPR
Instance of mother self-harming	MBR & NPR

Mother's number of psychiatric appointments	MBR & NPR
Father diagnosed with a psychiatric disorder	MBR & NPR
Instance of father self-harming	MBR & NPR
Father's number of psychiatric appointments	MBR & NPR
Head circumference at birth	MBR
Length at birth	MBR
Weight at birth	MBR
Pariety	MBR
Apgar at 10 minutes	MBR
Length of pregnancy in days (154-321)	MBR
Height at birth	MBR
Weight at birth	MBR
Number of cigarettes smoked at first prenatal care visit	MBR
Mother's body mass index at first prenatal care	MBR
Number of times moving housing in Sweden during the year	LISA
Family living together	LISA
Parent received sick/injury leave/benefit for more than 14 days	LISA
Parent received unemployment	LISA
Parent received study benefits	LISA
Parent received income support	LISA
Parent received study benefits	LISA
Living in a metropolitan area	LISA
Neighborhood deprivation scale	LISA
Level of parental involvement and knowledge in child's activities	SCM

4.1.3.4 Study IV

The predictors for Study IV were obtained from a combination of questionnaire data collected at two time points and genetic data (Tables 4.1.3.3 1-2). Data from CATSS came from A-TAC [171], the SDQ, SCM, Parent Child Relationship Inventory (PCRI) [173], and the Reactive-Proactive Aggressive behaviours Questionnaire (RPQ) [43]. The PCRI captures information on the parent child relationship and has acceptable test retest reliability, as well as good inter-rater reliability between the mother and child but not between father and child [174]. The RPQ differentiates the propensity for reactive and proactive aggressive behaviors in children and adolescents with good reliability and validity scores [43].

Analogous data from the NTR was obtained via the Child Behavior Checklist (CBCL) [175], Family Environment Scale (FES) [176], and the Youth Self-Report (YSR) [177]. The CBCL a standard measure for child psychopathology in epidemiology and has good convergence with the DSM [178]. FES is equivalent to the PCRI and has been found to have suitable performance metrics, with the exception of inadequate internal consistency [179]. The YSR was created to be an adolescent self-reported version of the CBCL and has acceptable reliability and validity measurements and corresponds well with the DSM [180].

The genetic data consisted of PGS and population stratification variables (Table 4.1.3.3 2). The PGS variables were obtained through GWAS for 17 traits related to psychiatric and biometric data. Leave-one-out summary statistics were created for GWAS which used CATSS and/or NTR data in the discovery sample. Additionally, a general p PGS score was created through combining the PGS variables related to psychiatric disorders or symptoms. Population stratification variables were included to account for the artefacts that may be arise from ancestry (described in detail in section 4.3.5).

Table 4.1.3.3 1. Questionnaire variables

Description	**Wave [1]**	**CATSS sources**	**NTR sources**
Sex		Single item	Single item
Birth year		Single item	Single item
ADHD symptoms	1	A-TAC	CBCL
Externalizing symptoms	1	A-TAC	CBCL
Internalizing symptoms	1	A-TAC	CBCL
Parents know child's after school activities	1	SCM	FES
Social difficulties	1	A-TAC	CBCL
ADHD symptoms	2	SDQ	YSR
Aggression	2	RPQ	YSR
Externalizing Symptoms	2	SDQ	YSR
Internalizing Symptoms	2	SDQ	YSR
Parent and child criticizes each other	2	PCRI	FES
Parent and child quarrel often	2	PCRI	FES
Social difficulties	2	SDQ	YSR
Has used marijuana	2	Single Item	Single Item
Has been drunk	2	Single Item	Single Item
Description		CATSS sources	NTR sources
Sex		Single item	Single item
Birth year		Single item	Single item
ADHD symptoms	1	A-TAC	CBCL
Externalizing symptoms	1	A-TAC	CBCL
Internalizing symptoms	1	A-TAC	CBCL
Parents know child's after school activities	1	SCM	FES

[1] Ages at the waves for the cohorts were as follows:

CATSS: 9 & 12, 15; NTR: 12, 16

Table 4.1.3.3 2. Included polygenic risk scores and genetic variables

Trait (reference)	Sample size
ADHD **[181]**	53,293
Aggression **[182]**	87,485
Anxiety disorders **[183]**	83,566
Anorexia Nervosa **[184]**	14,477
Childhood-onset asthma **[185]**	314,633
Autism **[186]**	46,350
Bipolar disorder **[187]**	51,710
Birth weight **[188]**	205,475
Childhood BMI **[189]**	39,620
Educational attainment **[190]**	746,714
Head circumference **[191]**	10,768
IQ **[192]**	269,867
Major depressive disorder **[193]**	332,580
Neuroticism **[194]**	390,278
Post-traumatic stress disorder **[195]**	174,659
Schizophrenia **[196]**	105,318
Subjective Well-being **[197]**	482,253 [1]
Population stratification principal components [2]	NA
General psychopathology score [3]	NA

Note: ADHD, Attention-deficit hyperactive disorder; BMI, Body Mass Index; IQ, Intelligence Quotient

[1] Rather than the entire well-being spectrum, summary statistics were recalculated to only include measures of life satisfaction and positive affect

[2] The first five genetic principal components as predictors in our model were included to account for the population stratification in the data.

[3] The general psychopathology score [77] was created by performing PCA analysis on the PCA-PGS scores related to mental health.

4.2 METHODS

4.2.1 Study Designs

4.2.1.1 Familial co-aggregation studies

Familial co-aggregation studies seek to uncover the extent to which familial factors, through environment and heritability, influence the development and co-occurrence of diseases [198]. These studies typically use logistic regression or survival analysis (described in section 4.3.1) within different groups of familial relationships, e.g., full siblings, half-siblings, cousins, and half-cousins, compared to non-related individuals. Then the effects of genetic or environmental influences can be interpreted from the results, as familial relationships share varying degrees of genetic and environmental factors [199]. Identical twins share 100% of their co-segregating alleles, while fraternal twins and full siblings share on average 50%. Siblings are expected to share similar environmental influences, e.g., family life. Half-siblings share on average 25% of their genetic influences and maternal half-siblings are expected to share more environmental influences, e.g., prenatal factors, than paternal half-siblings. Finally, cousins share 12.5% of their genetic influences and their half cousins even less. Thus, tracking the strength of the association estimates, e.g., hazard ratios, through the different family members can provide insight into the etiology of the outcome in question. For example, increased estimates throughout the familial relationships indicates a genetic influence. Additionally, if the estimates are higher in maternal half-siblings than paternal half-siblings it indicates that shared environmental influences are at play.

4.2.1.1 Machine learning studies

There are two main types of machine learning algorithms: supervised and unsupervised learning. Supervised machine learning algorithms classify data into pre-specified, known

outcomes. While in unsupervised learning algorithms the outcomes are not defined or nonexistent, the data is often grouped together into bins or clusters (as with nearest neighbors), or merely plotted (as in principal component analysis). Supervised machine learning models are particularly useful in large datasets where complex relationships may exist between the variables and the outcome.

Supervised machine learning models are usually trained and tested in several steps (Figure 4.2.1.1). First, the data is split into to two or more datasets: a training, a tune set (optional), and a test set. As the majority of machine learning methods require complete data observations, missing data is then imputed or dropped. Then, the model is first trained using the training set and optionally used to predict the tune set. Based on the performance on the tune set, the model's parameters are then tuned and retrained on the training data. Once one is satisfied with the model performance, the model is then tested on an independent test set. Preferably, an external separately collected, independently evaluated dataset, e.g., from different hospitals or countries, is used to determine the robustness of the model. Once the model has predicted the test and/or validation set it is not acceptable to modify the model, as to prevent inaccurate results arising from overfitting, i.e., the model fitting too closely to the dataset.

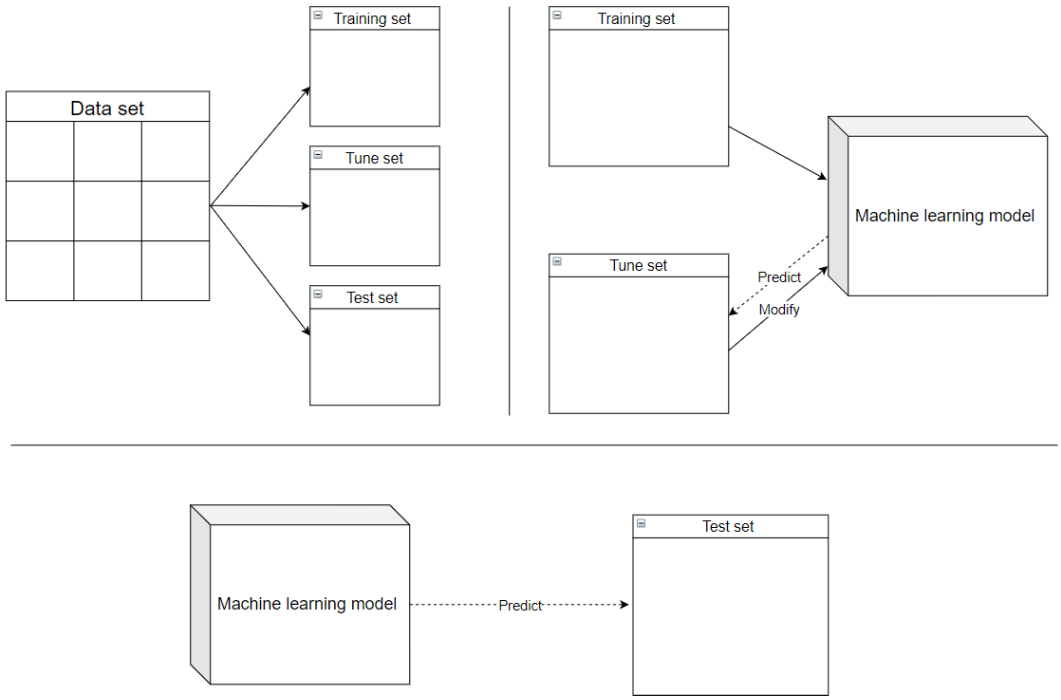

Figure 4.2.1.1. Flowchart of the machine learning pipeline. *First, the dataset is separated into a training, tune, and test set and the missing data in dropped or imputed. The model is first created using on the training set, then the model predicts the tune set. The model's parameters are modified based on the performance in the tune set and is then retrained on the training set. The process is completed until the model reaches a suitable performance. Then the model predicts the test set, the model cannot be modified after this step.*

Bias-variance trade off

One of the fundamental considerations during the model building process is the bias-variance trade-off, which is the desired balance of error in the model resulting from underfitting (too much bias) or overfitting (too much variance) [200]. Bias in this instance refers to the data not adhering to the assumptions of a model. In other words, the model is too rigid to properly account for the relationship between the predictors and the outcome. While variance is defined as the pliability of the model in relation to the data. Too much variance can lead the model to incorporate outliers or other data inconsistencies.

The balance of between bias and variance is reached by respectively decreasing or increasing model complexity during the parameter tuning process. Researchers must carefully consider their data in order to determine the parameters for their model. For example, the data for Study

IV was relatively simple, the training data contained ~5,000 participants and ~40 predictors, so we limited the complexity, i.e., variance, of the model when possible.

Parameter tuning

Cross-validation and validation in another dataset, i.e., using a tune set, are two common approaches to extrapolate how well the model will perform on new data during model tuning. Cross-validation breaks up data from the training set into a sub-training and tune set. Several types of cross-validation methods exist, but perhaps the most common is n-folds cross-validation. N-folds cross validation breaks up the training set into a certain number of sub-data sets with an equal number of data points in each fold; so in 5-fold validation 20% of the data points are held out as a test set in each round, with each data point left out once. In conjunction with this method one can then use the validation set as a pseudo test set to ensure that the model has not overfit to the training set.

Testing out a range of parameters for each model is typically done through random search or grid search. Random search chooses a parameter value randomly, out of a range of pre-specified values, for a certain number of rounds. Grid search tries all specified values for the parameters, so the number of search rounds becomes a factorial of each specified value. In general, random search can be useful for the initial stages of the parameter tuning process when one needs a sense of which might values work best, while grid search can be more useful to narrow down the values more precisely.

Data imputation

Missing data is not unique to machine learning and the question of how to handle missingness is a key point in any analysis plan. Three main types of missing data exist, missing completely at random, missing at random, and missing not at random. Missing completely at random indicates that there are not systematic differences between those with or without a missing variable; while missing at random means that the systematic differences that might be present

within the data are explained by other measured variables [201]. Finally, missing not at random indicates that the systematic differences that exist are explained by the variable itself and this difference is not explained by any other variable in the data [201].

The standard method to handle with missing data is to simply use the data as it is for approaches which allow missing data, however this is not possible for many algorithms, including machine learning. Therefore, researchers must either remove participants with incomplete data or replace, i.e., impute, missing data. Simply removing participants with incomplete data provides researchers with only the "true" values of variables, however the removal may bias the results and can drastically reduce sample size depending on the amount of missingness [202]. Thus, data imputation is often utilized in machine learning approaches.

Several approaches to data imputation exist, such as using the mean or median value of a variable, logistic regression, or machine learning algorithms. Study III used classification and regression trees (described in section 4.3.3.3). In Study IV we used K-nearest neighbors, this approach clusters k number of participants together based on their Euclidean distance and imputes the missing values based on the mean or mode (our study used the weighted average) [203]. Additionally, steps can be taken in order to reduce the bias that may occur within the imputation process: using multiple imputation, removing the outcome variable from the variables used for imputation, and imputing the learning sets and test set separately. Multiple imputation is frequently recommended and touted as the gold standard for improving imputation quality, and works by creating multiple complete datasets [204]. Different approaches exist, but in multiple imputation by chained equations each variable with missing data is imputed using an algorithm, e.g., logistic or linear regression, a specified number of times. The estimates produced from each model at each iteration are then averaged together [205].

Class imbalance

In data sets with few instances of the outcome machine learning models often classify all participants as the majority class, termed class imbalance. This often occurs with models that are trained on a small number of cases to compared non-cases [206]. Class imbalance is common in epidemiology and psychology where most outcomes are rare. Typically, it is accounted for through over-sampling the cases and/or under-sampling the controls when training the models. Weighting samples is one such technique, the weights for each class are typically determined by dividing the number in the majority class over the number in the minority class. For example, in a data set that had 10 individuals with depression and 100 individuals without depression, depressed individuals would have a weight of 10 while non-depressed individuals would have a weight of 1. These weights indicate that the model will resample each individual with depression 10 times during the model building process, while those without depression will only be sampled once. A weight of less than 1 would mean that some cases of that class would be removed, i.e., under-sampled. This method can be sensitive to outliers.

Boosting methods have also been devised for class imbalance. These methods adjust weights on the classes based on model performance, so that the class weights increase when the model has incorrectly classified a participant and decreases when the model correctly identifies a member of the class [206]. Thus, boosting methods focus on the “harder” class. However, this method can also be sensitive to outliers. SMOTEBoost is an oversampling technique that attempts to address this sensitivity [207], and works by imputing new instances of the minority class through randomly sampling a participant from the minority class. Next, an unsupervised machine learning technique, k nearest neighbors, is used to cluster the data points into similar groups of k size. Finally, new data points are imputed based on the surrounding data. Thus, this method can be considered less sensitive to outliers and creates more variation between the classes.

4.3 STATISTICAL APPROACHES

4.3.1 Survival Analysis

In short, survival analysis analyzes time-to-event-data, in which participants are monitored for an event over a period of time. This approach seeks to calculate both the event in question and the duration of time in which a participant was at risk. The data required for survival analysis includes the time of the start of follow up, time of the end of follow up, exposure(s) of interest, a categorical or binary event (such as diagnosis or death), and censoring. Censoring occurs when the follow up ends without an event, this could be due to death, drop-out, or simply the end of follow up. Thus, arising from censoring and event occurrence participants have different values for the time at end of follow up.

There are several estimates that can be calculated from survival analysis, however hazard rates, hazard ratios, and cumulative incidence are the focus on the present thesis. The hazard rate can be interpreted as the event rate at any time point on the time scale between the start and end date of follow up. The hazard ratio (HR) is then the ratio of the hazard rates for the exposed over the unexposed. A HR of 1 indicates that both the exposed and unexposed group had similar hazard rate of events, while a HR of 2 indicates that the exposed group had double the hazard rate of events. The cumulative incidence is the number of new events over the number of individuals at risk, i.e., those who are not censored or have the event, for a specified time (Figure 4.3.1). As the cumulative incidence is updated over time it is able to account for censoring.

Survival methods can be broadly classified into two types: parametric and non-parametric. Parametric models feature parameters which specify the survival times, whereas non-parametric models, e.g., Cox proportional hazards model, do not make assumptions on the distribution of the survival time nor on the hazard. Typically non-parametric models are standard in medical epidemiology.

The Cox proportional hazards model is the main survival method utilized in this thesis [208]. This method produces HRs but does not estimate the baseline hazard, which is the hazard when covariates are set to zero or another specified level. As a result the model cannot estimate absolute estimates, such as cumulative incidence, unlike the Kaplan-Meier method. The Kaplan-Meier is another non-parametric model that estimates survival time and is relatively robust against censoring [209].

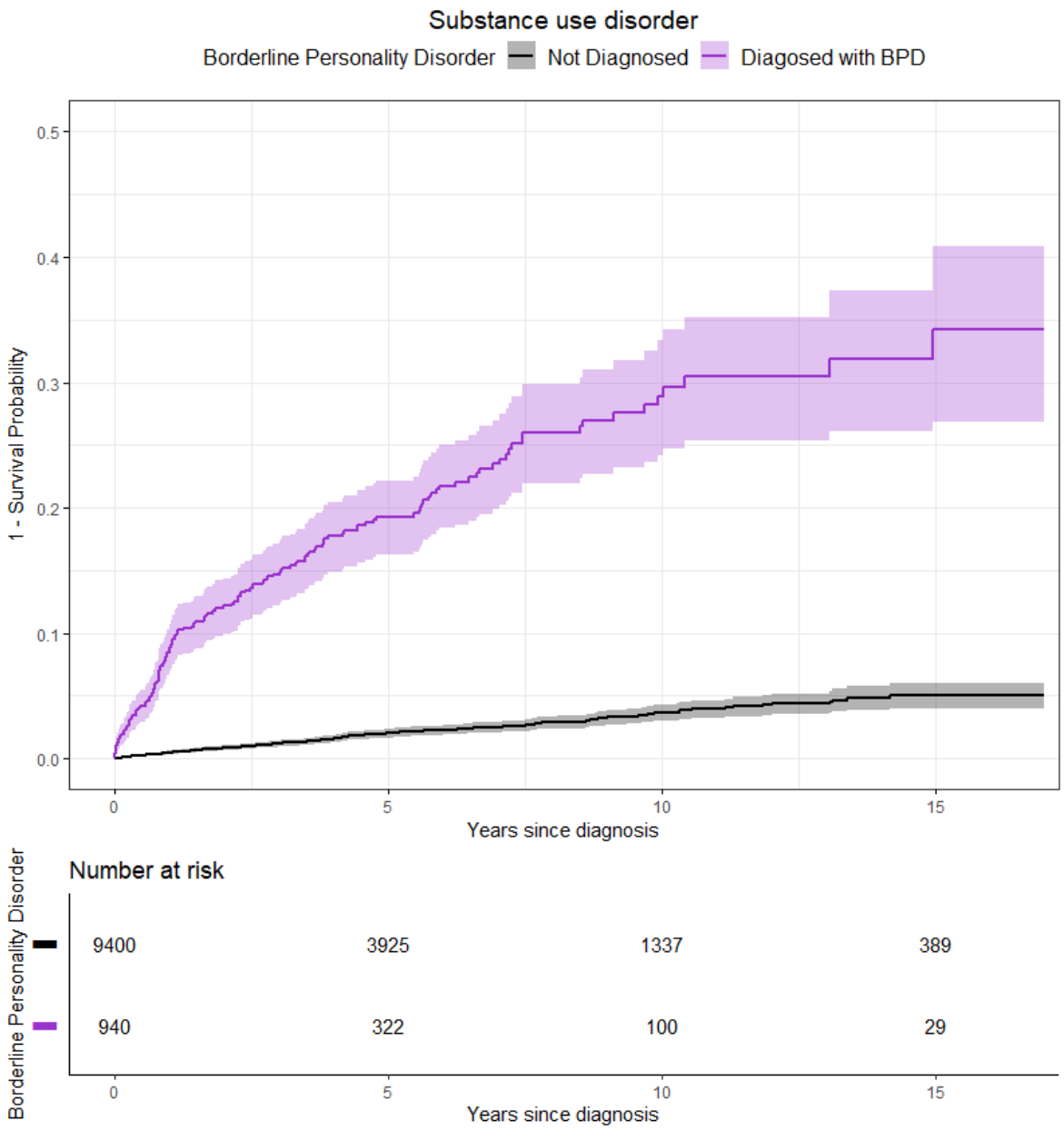

Figure 4.3.1. Sample 1-survival curve with data from study III. *The Kaplan-Meier survival curve follows males in the Swedish National Registers for a maximum of 18 years. Individuals were considered exposed on the date of a borderline personality disorder diagnosis and followed until the date of censoring or receiving a substance use disorder diagnosis.*

Unexposed individuals were matched to borderline personality disorder 10:1 based on sex and birth year. Follow up for matched individuals began on the same date as their borderline personality disorder exposed counterparts. The number at risk represents individuals who have not yet been censored or had the outcome at the time point in years.

4.3.2 Unsupervised Machine Learning Models

Unsupervised machine learning methods seek to identify structure or patterns within the data, rather than to classify outcomes. Multiple approaches exist, for example k-means clustering which clusters the dataset into k number of clusters [210]. However, principal component analysis was the method utilized within this thesis.

4.3.2.1 Principal Component Analysis

Principal component analysis is a commonly used unsupervised machine learning technique (Figure 4.3.2) [211]. This method can be especially useful for visualizing the data and allows for an approximation of how well supervised learning models can be expected to perform on the dataset. In brief, it reduces the dimensionality of the dataset while preserving as much variability (information) as possible by creating linear combinations of predictors. The resulting principal components are uncorrelated and each can explain an amount of variation in the dataset, with the first principal component representing the highest amount of variation.

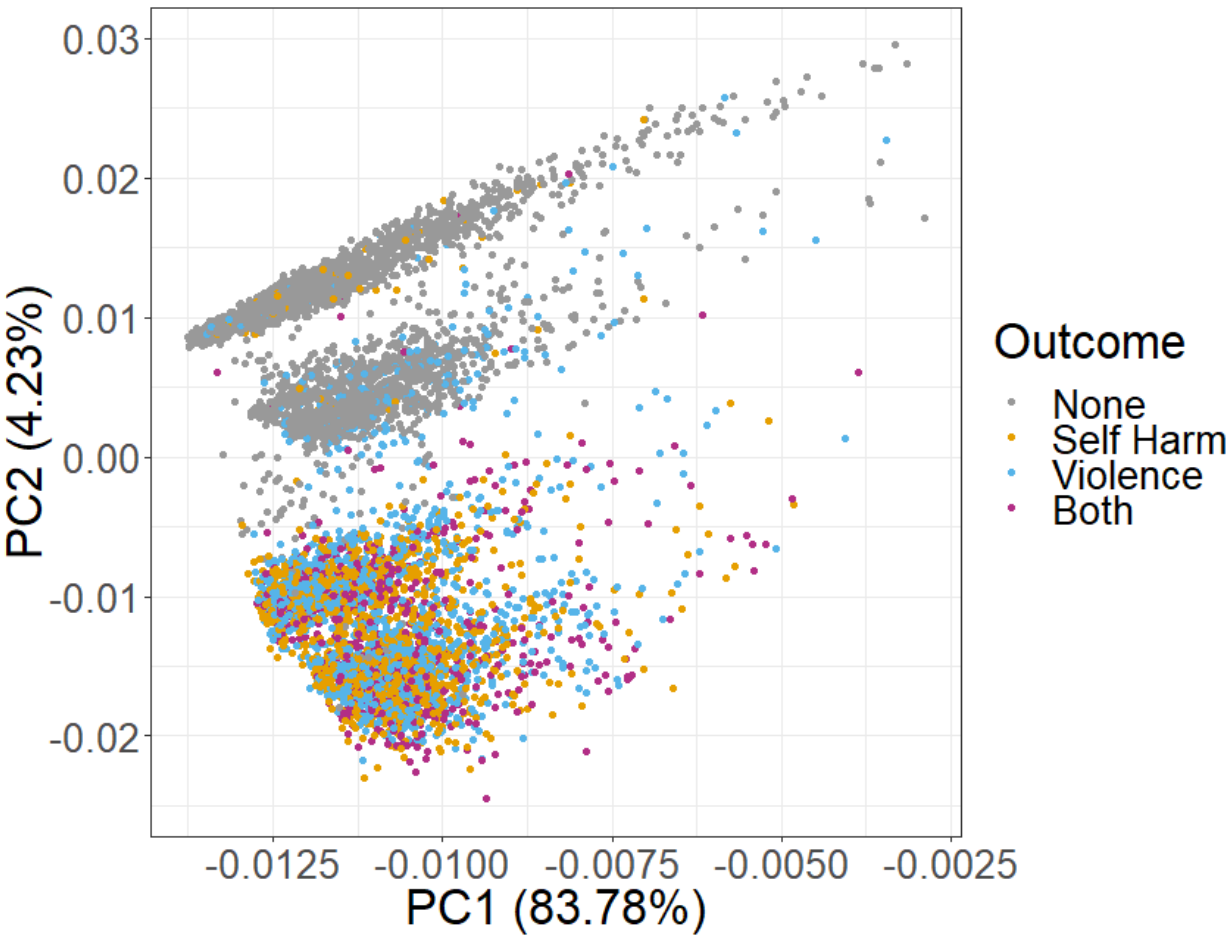

Figure 4.3.2. A sample principal component analysis plot with toy data, principal component (variance explained). *The scatter plot shows the data separated by indicated principal components. The variance explained by each principal component is indicated in parentheses. The dots represent different participants and the distance represents the relative variance between the participants*

4.3.3 Supervised Machine Learning Models

4.3.3.1 Logistic regression

Logistic regression is the classic method for analyzing binary outcomes in epidemiology [212]. In this method the relationship between the predictors and the outcome is expected to be linear on the log-odds scale. The predictors are each assigned a regression coefficient which describes the change of the log-odds for the outcome for each unit change of the predictor. The performance of this method can be improved through a process called regularization, which works by reducing the variance, i.e., dimensionality, of the model. In regularization the regression coefficients are "shrunk" towards zero based on the least square residuals, i.e.,

lowest value within the sum of squared residuals (also termed the sum of the squared errors), through a process called shrinkage. Several modified versions of logistic regression utilize this method such as LASSO, ridge regression, and elastic net.

4.3.3.2 Shrinking approaches

Ridge regression creates a penalty using lambda, commonly referred to as L2 (λ_2), by multiplying L2 with the square of the predictor's coefficient and adding that product to the sum of the squared residuals, which is the unexplained variance (error) in the model. Ridge regression aims to minimize or "shrink" this equation:

$$\textit{Sum of squared residuals} + \lambda_2 \times (coef_1^2 + \ldots + coef_n^2)$$

LASSO works similarly, but uses a lambda value L1 (λ_1) to create its penalty; additionally L1 is multiplied by the absolute value of the coefficients.

$$\textit{Sum of squared residuals} + \lambda_1 \times (|coef_1| + \ldots + |coef_n|)$$

Functionally, the primary difference between these methods is that lasso can shrink poorly predicting variables' coefficients to 0 thus dropping them from the model, while ridge regression only shrinks the coefficients to near 0. In practical terms this means that lasso tends to outperform ridge when many predictors are uninformative, while ridge regression tends to outperform lasso where predictors are carefully chosen.

Elastic net combines these two models into one equation, and is especially beneficial when dealing with a high degree of correlated variables. This method groups and regularizes, i.e., shrinks, the correlated variables, while ridge regression merely assigns identical weights. These methods are especially useful in the variable selection process of the model building steps, typically variables with coefficients that are forced to or near 0 are then removed from the dataset by the analyst.

4.3.3.3 Tree-based models

Tree-based algorithms are comprised of decision trees which separate data points into hierarchical structures based on yes-no binary decisions (Figure 4.3.3.3). Each decision point, i.e., node, is comprised of a randomly sampled predictor, and categorical or continuous variables are automatically transformed into binary variables. Decision trees consists of three types of nodes: the root node, the internal nodes, and leaf nodes. Participants are broken down into subgroups at each root node and into subsequent internal nodes until the subgroup has been uniformly categorized into an outcome class at the leaf node. The subgrouping continues until there are a specified number of layers of internal nodes between the parent node and the leaf nodes, and/or until the leaf nodes have reached a specified minimum number of participants.

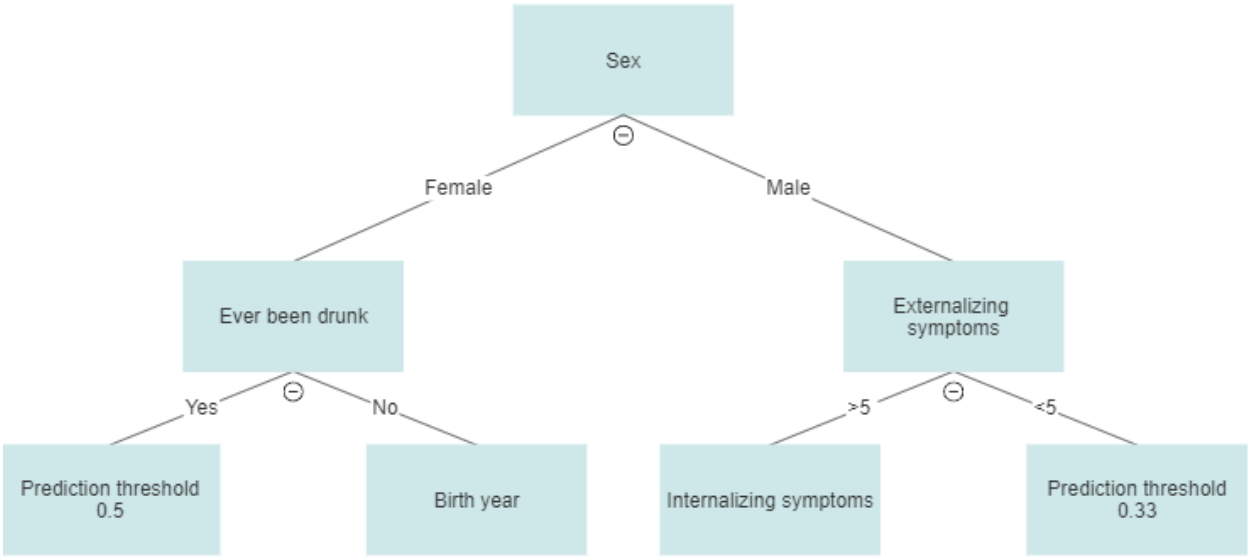

Figure 4.3.3.3. A sample decision tree with example predictors from study IV. *This follows the classification of each participant. Each decision tree is comprised of a root node (sex), internal (other predictors) and leaf nodes (prediction thresholds). The leaf nodes need not end at the same "level".*

The tree-based models used studies III & IV (Random Forest, Gradient Boosted Machines, and eXtreme Gradient Boosting [XGBoost]) aggregate multiple decision trees. Each tree contains a certain subset of the data rows, this can be done with or without replacement. In a random forest model the trees are trained in parallel, thus information from each of the decision trees is not shared with the other during the tree building process. The ultimate classification of the participant is usually determined by majority voting [213]. On the other hand, gradient boosting machines are trained sequentially, incorporating information on the previous tree's error, i.e., residuals, based on the loss function. In other words, the model aims to optimize the loss function through gradient descent. Here, gradient is defined as the sum of the derivative of the loss function in regards to each predictor. While gradient boosted machines provides more data than random forests, the model's added complexity means that it is more prone to overfitting and computationally expensive. As indicated by its name, XGBoost is a type of gradient boosted machine. This model was developed to improve the efficiency and computational time of the standard gradient boosted machines [214].

Variable importance

Tree-based models can provide insight into the usefulness of each predictor through variable importance scores. These scores are calculated using different approaches, e.g., [213, 215, 216], but can broadly be interpreted as the decrease in model performance when the variable is modified (typically randomized) or removed. Thus, the higher the difference in score, the more important the variable. Gini importance, another common method to measure the "usefulness" of the variable, calculates the number of times a variable was used to split a node weighted by the number of participants it splits [213]. However, variable importance is by far the most common.

The interpretation of variable importance scores must be done with care. Machine learning algorithms, and by proxy variable importance, cannot give insight into the nature of causality

or indicate a direct effect between the predictors and the outcome [217]. Furthermore, the score cannot give information on the direction of the association between a variable and the outcome. Although efforts have been made, no suitable test exists to determine statistical significance of variable importance scores [218]. Thus, the interpretation of variable importance scores are limited to a descriptive ranking of the variables. An arbitrary number of top variables or variables which meet a chosen cut-off may then be chosen for additional follow up.

Several biases may affect the ranking of variable importance scores. First, variable importance scores can be biased towards categorical variables with more levels compared to binary or continuous variables. Scaling and sampling without replacement can reduce can mitigate this bias [219]. Additionally, if the data contains groups of correlated variables the groups will be "clumped" together and the importance scores will be biased towards smaller groups [220]. This bias can be minimized by combining like variables. Additionally, it can be mitigated through increasing the number of trees (a suggested rule of thumb is to multiply the number of variables in the model by 10), although a high number of trees can cause overfitting in the tree-model itself.

4.3.3.4 Support vector machines

Support vector machines classifies data in three steps (Figure 4.3.3.4) [221]. First, the data is clustered based on the number of classes using an unsupervised machine learning approach. The data points in the clusters are called vectors. Next, a line (termed a hyperplane) is drawn by first finding the support vectors, defined as the closest data points between the two class clusters. Then, the algorithm finds the maximum distance between the support vectors and there creates the hyperplane. With non-linear SVM approaches similar steps take place, however data is transformed into a higher dimensional space using a process called kernelling. Several kernelling methods exist, such as the polynomial kernel which creates new predictors based on applying polynomial combination on all predictors. The model then creates a non-linear hyperplane using the polynomial features.

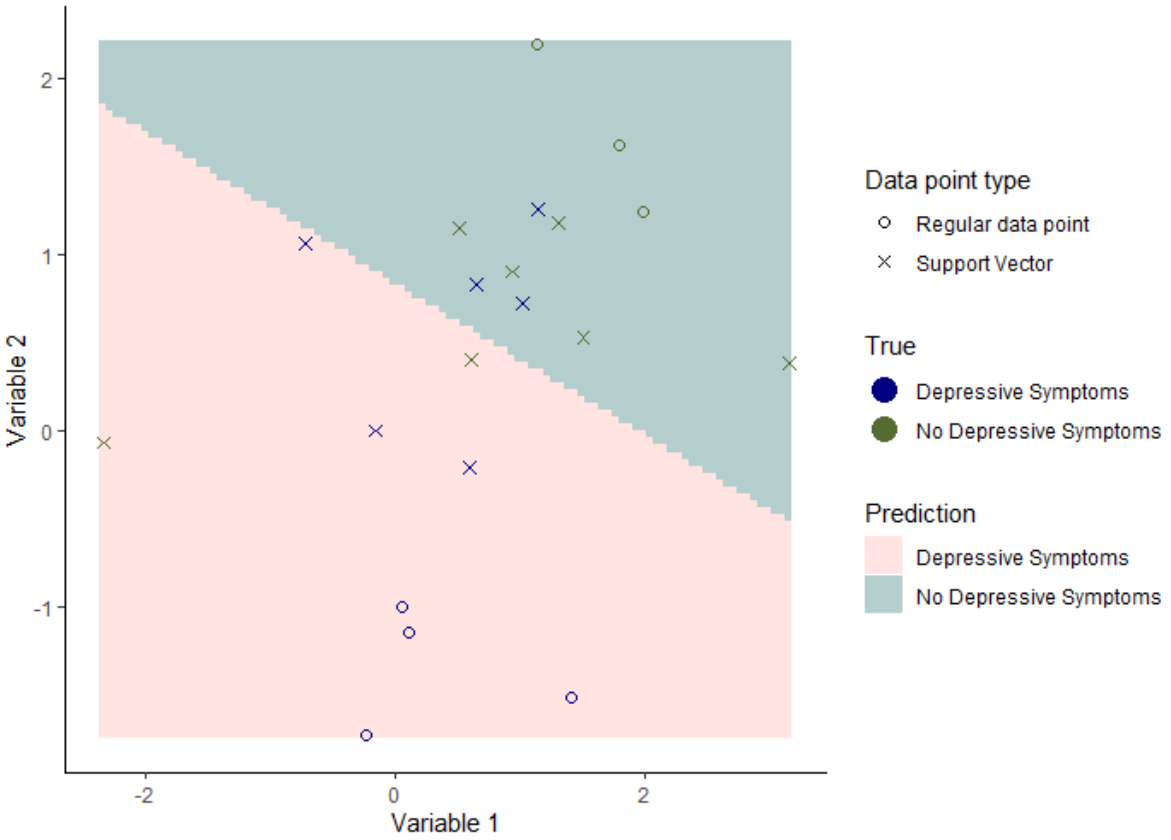

Figure 4.3.3.4. A sample support vector machine. *In this example two variables were used to predict the outcome. The hyperplane (or line separating the predicted classes) is determined by finding the maximum distance between closest data points of the two classes. These closest data points are referred to as support vectors. This model classifies new data points based on their location in relation to the hyperplane.*

4.3.3.5 Neural network

This method uses interconnected processors, or neurons, organized into an initial input layer, one or more hidden layers, and an output layer (Figure 4.3.3.5) [222]. During model building the data is fed into the neurons in the input layer, then in the following layers the neurons receive input from the previous layer as weighted averages. The neuron then sums the weights and passes them to an activation function, for example a logistic function (termed sigmoid activation function) or more commonly a reticular linear activation function. A reticular linear

activation function accounts for interaction effects between predictions and as well as non-linear values.

After passing through the hidden layers, these weights are summed and the final classification takes place. Although the standard direction of the signal through the model is forward, several directional variations exist such as back propagation [223]. Back propagation follows the same process as a standard neural network, however when the signal reaches the end of the network a back-propagation algorithm feeds the error back through the model for additional readjustment until little to no improvement is made or it reaches a specified number of rounds.

Although this method is frequently referenced when speaking about machine learning, key drawbacks exist. First, neural networks are traditionally referred to as a “black box” method as no information is given on the nature of the connections between the layers. Albeit, advancements have been made to improve the interpretation of this approach such as Shapley additive explanations and the Gideon method which can provide an analogue to variable importance scores [224, 225]. Second, Neural networks are complex and thus require more statistical power than other machine learning types; meaning that they are less suitable for smaller data sets.

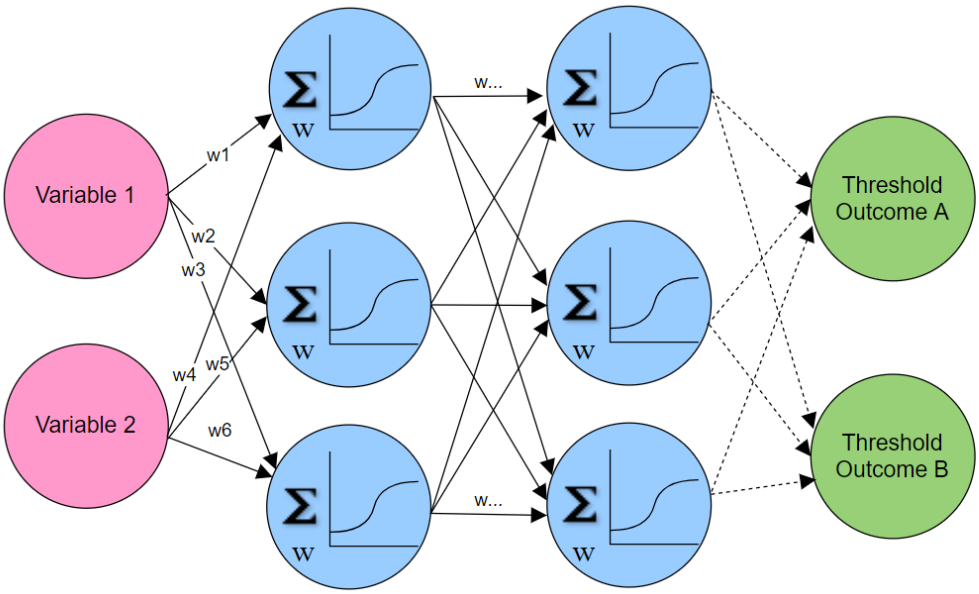

Figure 4.3.3.5. A sample neural network. *This diagram contains an input layer (pink), two hidden layers with three nodes (blue), and an output layer (green). The hidden layers receive information from the previous layer as a weighted average, these weights are then summed and passed through the activation function (in this example logistic regression).*

4.3.4 Performance Metrics

4.3.4.1 Area under the receiver operating characteristic curve

Area under the receiver operating characteristic curve (AUC) was the primary metric used to determine the prediction model performance for this thesis [226, 227]. At its core the AUC derives from a confusion matrix, which contains four squares: true positive, false positive, true negative, false negative (Table 4.3.4.1). From these values several metrics can be obtained, such as the sensitivity, i.e., how well the model categorizes individuals that have the outcome and specificity, which is how well the model correctly categorizes individuals that *do not* have the outcome.

Table 4.3.4.1. A sample confusion matrix.

	Aggressive	Not aggressive	
Classified Aggressive	True Positive (TP) 185	False Positive (FP) 186	Positive Predictive Value 0.498 $\frac{TP}{TP + FP}$
Classified Not aggressive	False negative (FN) 263	True negative (TN) 1341	Negative Predictive Value 0.836 $\frac{TN}{TN + FN}$
	Prevalence 0.192		
	Sensitivity 0.413 $\frac{TP}{TP + FN}$	Specificity 0.878 $\frac{TN}{FP + TN}$	

This table shows a sample confusion matrix with the calculation of several performance metrics

However, prediction models return the probability of a participant being in a certain class rather than a binary answer, so a threshold must be selected in order to classify a participant thus completing the confusion matrix. The receiver operating characteristic (ROC) curve (Figure 4.3.4.1) visually plots the trade-off between the sensitivity and 1 – the specificity across the different prediction thresholds. The AUC is the area under the ROC, and aggregates the performance across the prediction thresholds. Generally, AUC > 0.9 suggests excellent model prediction and is the desired performance for medical use, 0.8-0.9 is good, 0.7-0.8 is fair, and <0.7 is poor [228]. However, this rule of thumb is context specific and thus does not always translate to clinical utility. In Study IV, the use of a multi-class model meant that we were unable to traditionally calculate an AUC, thus the macro AUC was presented. The macro AUC is calculated by first turning each of the classes into binary outcomes so that each class receives its own binary AUC, e.g., suicidal behaviors, aggressive behaviors, both, or neither, would be

translated to suicidal behaviors vs all other classes and so on. Next, the AUCs are averaged together to form the macro AUC.

The AUC is not without its downsides, for example it does not account for contexts where a high sensitivity or specificity is more desirable than the other [229], which highlights the importance of considering the AUC in the context of other performance measures such as the sensitivity, specificity, positive predictive value (the probability that a positive classification was correct) and negative predictive value (the probability that a negative classification was correct).

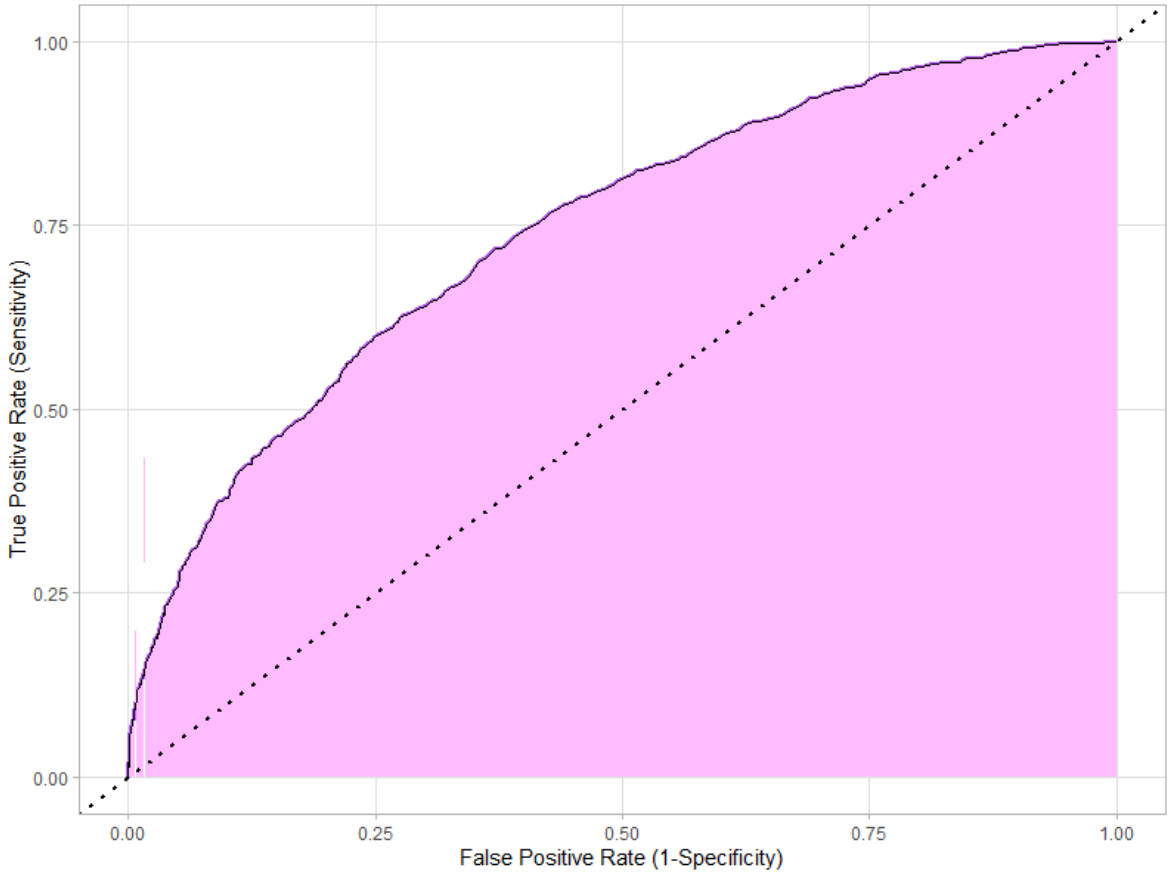

Figure 4.3.4.1. A sample receiver operating characteristic curve. *This ROC curve shows the sensitivity and 1- specificity across a series of prediction thresholds. The diagonal line represents performance no better than chance. The AUC is represented by the shaded area.*

4.3.5 GWAS and Polygenic risk scores

As described previously, GWAS measures the association between each of the SNPs and the outcome. Summary statistics can be obtained from GWAS which contain the results of the regression, e.g., effect size, standard error, p-value, and sample size, for each of the SNPs analyzed [136]. Using the summary statistics the PGS can be estimated in a target sample. However, the target sample must be independent of the data used to create the summary statistics to prevent a biased result. The PGS are estimated for each individual in the target sample by multiplying the effect size of the risk allele in each SNP, times the number of risk alleles the individual carries. The results are then added together across the genomic loci throughout the genome [230].

To improve the accuracy of PGS researchers must account for the sample size of the original GWAS, the SNP heritability, and general genetic architecture (such as population stratification and linkage disequilibrium). Population stratification refers to the variations in allele frequencies that arise from between differing ancestries, e.g., Northern vs Southern Europe. Therefore, if not correctly accounted for allele frequency differences unrelated to the outcome may show up as statistically significant between the cases and controls. As offspring inherit DNA in a sequence of "chunks" from their parents, sequences which exist in their parents are often retained. Thus, alleles are dependent on their proximity to each other along the chromosomes. The correlation between alleles at close proximity is referred to as linkage disequilibrium.

There are several methods to account for linkage disequilibrium such as LASSO (described in section 4.3.3.1) and LDpred [231]. LDpred uses a Bayesian model to account for inflated effect sizes that might occur from linkage disequilibrium. The posterior mean, i.e., the mean of a distribution informed by the data, of the SNP effect sizes are then conditioned on the genetic architecture from an independent reference panel, e.g., 1000 genomes data. As not every SNP within the genome is causal to the trait in question, one must determine which SNPs to include

in the PGS. Traditionally, SNPs that have reached a certain specified p-value thresholds in the GWAS are included in the risk score calculation.

4.4 ETHICAL CONSIDERATIONS

The primary ethical concerns for my research project are data privacy, data interpretation, and preserving human dignity. First and foremost, the data from the Swedish registers are anonymized and minimally invasive to participants, therefore no consent form is needed from individual participants [232]. The benefits of the results of the studies derived from this data are beneficial to society as a whole, and thus mitigate the potential ethical discomfort from the lack of individual consent forms. Although the data are anonymized, identification through register linkages are possible in some circumstances, thus requests to use data are heavily vetted. Careful measures must be taken to ensure data privacy and to preserve the anonymity of the participants. In order to preserve the security of the data several steps were taken: the datasets derived from register data have stayed on KI servers, the files containing the data are only available to authorized users on password protected accounts.

A substantial amount of the data comes from the Child and Adolescent Twin Study in Sweden, a subset of the Swedish Twin Registry data [159]. This means that the data collection was slightly more invasive to participants than the national registers, through the means of lengthy questionnaires and DNA samples. Parents and their children were required to fill out consent forms during the first data collection. The addition of DNA samples adds another layer of importance to data privacy as DNA data is uniquely identifiable to individual persons. A leak involving this data would represent a significant breach of privacy for both the participants and their family [233]. This means that extra care and steps must be taken to ensure that the data is kept secure. As the field is still relatively young in comparison to other more established fields, a major breach in data by a research institution could irrevocably damage public trust and reduce participation in studies across the field. Care to preserve anonymity has been taken by keeping raw data on a secure server without connection to the internet, only authorized users

can access this server with two-factor identification. All data derived from this data are kept on secure KI servers on password protected accounts.

4.4.1.1 Data Interpretation

Care must be taken to both interpret and communicate the results of the study accurately. First, the formulation of one's research question must take into account limitations of one's data and the tenets of causality. Cautiously inferring causality is especially important in the field of epidemiology, where controlled experiments are uncommon. Thus posing causal questions using only health care data could lead to an incorrect interpretation of the results without proper context and methodology. This nuance is often lost in popular science articles, such as the commonly referenced association between red wine and a reduction of heart disease [234]. Due to inaccurate reporting many laypersons believe that red wine *causes* the reduction of heart disease, rather than merely being an association. This could have inadvertently led to adverse health consequences through individuals increasing their red wine intake.

Additionally, researchers have a duty to thoroughly report of the strengths and weakness of their work. No study is without bias, and taking these into account only helps one get closer to the truth. Moreover, understanding how to communicate these results to lay persons in a clear but precise manner is a crucial step to ensuring that one's work is not taken out of context.

4.4.1.2 Preserving Human Dignity

The most critical ethical concern for my work is the preservation of human dignity. This concern is deeply rooted in the historical and present context of behavioral genetics. Behavioral genetics is a relatively young field in comparison to other research areas, beginning a little less than 100 years ago by Francis Galton [235]. In its infancy it was commonly termed as race biology or racial hygiene and advocated racial superiority and eugenics, or the idea that human evolution is stifled without an emphasis on selective breeding [236]. While American researchers led the charge, Sweden and the Karolinska Institutet in particular are also

implicated in this movement [237]. Notably, there is even a street on campus named after one of the most prolific advocates for eugenics and racial superiority, Gustaf Retzius, whom measured the skulls of different humans in an effort to prove the "grandness of the Nordic race" [238]. Additionally, the founder for the Swedish State Institute for Racial Hygiene, Herman Lundborg completed his PhD from Karolinska.

The findings produced from this period were poorly conducted and methodologically flawed through highly selected samples and arbitrary criteria for the definition of superiority [239]. Beyond promoting misleading pseudoscience, the findings produced from this period supported the forced mass sterilization of persons deemed unworthy to reproduce; and ultimately the genocide of 6 million persons in Germany only 70 years ago. The effects of this ideology have long since continued, as the Swedish government supported the sterilization of individuals with intellectual disability until 1976 [240]. And more recently, individuals who sought treatment for gender dysphoria, i.e., people who are transgender, were forcibly sterilized in Sweden until 2012. Racism and dehumanization of vulnerable persons have been intertwined in the field of human genetics since its inception. How does one today carry forth research in this context knowing the horrors of misinterpretation and hijacking of scientific inquiry? The answer is complex and critical for researchers to justify.

Scientists should not shy away from asking questions or seeking answers to controversial topics, however this comes with an important caveat: the questions themselves should not be value laden. To say a question is value laden implies that personal values or opinions have shaped the question and thus will shape the answer [241]. For example, the question "Which sex is smarter, men or women?" is value laden because it implies that one holds the belief that one sex is smarter than the other. Avoiding these types of questions can be difficult simply because one might not recognize the many ways that beliefs and opinions can creep into to their own work, especially since science has the reputation as being a neutral field. However, scientific inquiry is only as neutral as the scientists working towards the answer. Due to the

sensitivity and historical background of behavioral genetics, researchers must keep an even closer eye on their questions and preconceived opinions.

One such example of unforeseen racial bias exists within machine learning models [242]. One such model working to allocate hospital treatment based on disease severity, considered black patients' symptom scores as less severe than their white counterparts thus leading to withholding of treatment [242].This did not arise from nefarious circumstances, but instead from biased data related to health care costs. Black patients in the US are less insured than their white counterparts. The potential for racial bias within the variable for healthcare costs was overlooked by researchers and clinicians alike, this highlights the importance of considering the types of variables one includes in the model.

Beyond the scientists own values and opinions, behavioral geneticists also have a responsibility to inform society and participate in debates with those seeking to justify racist beliefs with the results given from these studies. Thus, public outreach and accessibility to laypersons is critical for behavioral geneticists and essential for preventing the mistakes of the past [243]. To this end, I have personally petitioned the Solna government to change the name of Retzius väg. While we should not forget the detrimental work he has done, KI cannot allow his name to hold a place of honor on campus. In conjunction with the efforts of several activists groups, KI has agreed to change the name of the street.

5 RESULTS

5.1 STUDY I

5.1.1 Descriptive Statistics

This study included individuals from Sweden and Denmark identified from their respective national registers. The Swedish sample consisted of 2,517,260 individuals and contained 15,923 (45.79% female) individuals diagnosed with T1D and 27,333 (93.80% female) diagnosed with any eating disorder (AED). The Danish sample (n = 1,825,920) included 6,575 (46.87% female) patients diagnosed with T1D and 27,333 (93.60% female) diagnosed with AED.

5.1.2 Main Findings

In both samples, individuals with T1D had a greater risk of being diagnosed with each eating disorder category (HR [95% CI] Sweden: AED 2.02 [1.80 – 2.27], anorexia nervosa (AN) 1.63 [1.36 – 1.96], other eating disorder besides anorexia nervosa (OED) 2.34 [2.07 – 2.63]; Denmark: AED 2.19 [1.84 – 2.61], AN 1.78 [1.36 – 2.33], OED 2.65 [2.20 – 3.21]) (Table 5.1.2). The results of the meta-analysis of the Danish and Swedish cohorts reflected the congruent findings between the cohorts (AED 2.07 [1.88 – 2.28], AN 1.68 [1.44 – 1.95], OED 2.44 [2.17 – 2.72]).

In the Swedish sample, full siblings of patients with T1D had a greater risk of being diagnosed with each eating disorder category (AED 1.25 [1.07 – 1.46], AN 1.28 [1.04 – 1.57], OED 1.28 [1.07 – 1.52]). As a sensitivity analysis, we repeated the full sibling analysis in the Swedish cohort using only T1D diagnosis from the ICD-10 and found results consistent to the main analysis (AED 1.24 [1.06 – 1.44], AN 1.28 [1.04 – 1.56], OED 1.26 [1.06 – 1.50]). However, in the Danish analysis the same results each had CIs which contained 1 (AED 1.01 [0.78 – 1.32], AN 1.14 [0.80 – 1.62], OED 0.98 [0.71 – 1.36]). All other familial analyses had confidence intervals which contained 1.

Table 5.1.2. Within individual and familial co-aggregation between type 1 diabetes exposure and subsequent eating disorders, hazard ratios[1] (95% confidence intervals)

Sweden	Number of individuals	Individuals with type 1 diabetes	Number of pairs of relatives[2]	Any Eating Disorder N (%)	Anorexia Nervosa N (%)	Other Eating Disorder N (%)
Within individual	2 517 260	15 923 (0.63%)	NA	**2.02 (1.80 – 2.27)*** 26 840 (1.07%)	**1.63 (1.36 – 1.96)*** 12 573 (0.50%)	**2.34 (2.07 – 2.63)*** 20 911 (0.83%)
Full siblings	1 789 806	11 473 (0.64%)	1 336 734	**1.25 (1.07 – 1.46)*** 20 092 (1.12%)	**1.28 (1.04 – 1.57)*** 9 581 (0.54%)	**1.28 (1.07 – 1.52)*** 15 552 (0.87%)
Half siblings	492 133	3 041 (0.62%)	453 863	**1.05 (0.80 – 1.39)** 5 681 (1.15 %)	**1.15 (0.75 – 1.77)** 2 367 (0.48%)	**0.99 (0.73 – 1.35)** 4 630 (0.94%)
Full cousins	1 952 785	12 748 (0.65%)	4 761 929	**1.10 (1.00 – 1.20)** 21 694 (1.11%)	**1.08 (0.98 – 1.19)** 10 347 (0.53%)	**1.12 (0.98 – 1.27)** 16 810 (0.86%)
Half cousins	510 050	3 313 (0.65%)	947 500	**0.97 (0.79 – 1.20)** 5 558 (1.09%)	**0.81 (0.57 – 1.16)** 2 430 (0.48%)	**1.05 (0.85 – 1.32)** 4 469 (0.88%)
Denmark						
Within individual	1 825 920	6 559 (0.36%)	NA	**2.19 (1.84 – 2.61)*** 18 683 (1.02%)	**1.78 (1.36 – 2.33)*** 9 271 (0,51%)	**2.65 (2.20 – 3.21)*** 12 875 (0.71%)
Full siblings	1 300 833	4 771 (0.37%)	934 967	**1.01 (0.78 – 1.32)** 13 437 (1.03%)	**1.14 (0.80 – 1.62)** 6 825 (0.52%)	**0.98 (0.71 – 1.36)** 9 127 (0.70%)
Half siblings	375 026	1 297 (0.35%)	340 033	**0.74 (0.44 – 1.25)** 4 462 (1.19%)	**1.07 (0.56 – 2.07)** 2 049 (0.55%)	**0.84 (0.48 – 1.49)** 3 227 (0.86%)
Full cousins	1 214 978	4 566 (0.38%)	2 958 609	**0.97 (0.83 – 1.13)** 12 472 (1.03%)	**1.04 (0.85 – 1.29)** 6 439 (0.53%)	**0.92 (0.76 – 1.11)** 8 404 (0.69%)
Half cousins	226 105	824 (0.36%)	390 693	**0.64 (0.33 – 1.23)** 2 191 (0.97%)	**0.90 (0.41 – 1.94)** 1 081 (0.48%)	**0.67 (0.31 – 1.46)** 1 526 (0.67%)
Meta-analysis						
Within individual	4 343 180	22 482 (0.51%)	NA	**2.07 (1.88 – 2.28)***	**1.68 (1.44 – 1.95)***	**2.44 (2.17 – 2.72)***

[1] Adjusted for sex and birth year of index individual and relative (when applicable).
[2] Number of unique pairs
*CI does not contain 1

5.2 STUDY II

5.2.1 Descriptive Statistics

A total of 1,969,839 Swedish born individuals were included in the study and 12,175 (85.3% female) were diagnosed with BPD. Absolute values for each of the indicators can be found in Tables. 5.2.1 1-3. The mean age at the end of follow up was 29.69 years.

Table 5.2.1 1. Absolute number of psychiatric disorder diagnoses

Indicators	Total No. %		Diagnosed with BPD No. %		Not Diagnosed with BPD No. %	
Affective disorders	13,265	0.7%	1,962	14.5%	11,303	0.6%
Anxiety	122,538	6.2%	10,184	75.4%	112,354	5.7%
Attention deficit hyperactive disorder	43,310	2.2%	3,638	26.9%	39,672	2.0%
Autism spectrum disorder	19,779	1.0%	1,108	8.2%	18,671	1.0%
Bipolar disorders	18,603	0.9%	3,267	24.2%	15,336	0.8%
Conduct disorder	4,135	0.2%	407	3.0%	3,728	0.2%
Depression	113,685	5.8%	9,394	69.6%	104,291	5.3%
Dissociative disorders	16,992	0.9%	1,478	10.9%	15,514	0.8%
Eating Disorders	15,496	0.8%	1,532	11.3%	13,964	0.7%
Intellectual disability	2,277	0.1%	13	0.1%	2,264	0.1%
Obsessive compulsive disorder	15,455	0.8%	1,399	10.4%	14,056	0.7%
Personality disorders (PD)	19,889	1.0%	5,667	42.0%	14,222	0.7%
PD: Antisocial personality disorder	1,246	0.1%	328	2.7%	918	0.0%
PD: Avoidant personality disorder	1,683	0.1%	278	2.3%	1,405	0.1%
PD: Not specified personality disorder	12,657	0.6%	3,779	30.8%	8,878	0.5%
Post-traumatic stress disorder	10,326	0.5%	1,961	14.5%	8,365	0.4%
Psychotic disorders	32,693	1.6%	5,577	34.2%	27,116	1.4%
Psychotic: Schizophrenia	10,959	0.6%	1,950	12.0%	9,009	0.5%
Psychotic: Schizoaffective disorder	20,715	1.0%	4,382	26.9%	16,333	0.8%
Psychotic: Schizotypal disorder	1,802	0.1%	793	4.9%	1,009	0.1%
Substance use disorder	90,577	4.6%	6,218	46.1%	84,359	4.3%
Tic disorder	3,232	0.2%	87	0.7%	3,145	0.2%

Table 5.2.1 2. Absolute number of somatic illness diagnoses

Indicators	Total No.	%	Diagnosed with BPD No.	%	Not Diagnosed with BPD No.	%
Asthma	101,682	5.2%	1,302	10.7%	100,380	5.1%
Autoimmune disorders [a]	103,814	5.3%	1,134	9.3%	102,680	5.2%
Autoimmune: Intestinal malabsorption	14,357	0.7%	168	1.4%	14,189	0.7%
Autoimmune: Psoriasis	21,816	1.1%	23,	1.9%	21,578	1.1%
Autoimmune: Ulcerative collitis	14,398	0.7%	101	0.8%	14,297	0.7%
Cardiovascular disorders (CVD)	46,350	2.4%	598	4.9%	45,752	2.3%
CVD: cardiac arrhythmias	3,238	0.2%	38	0.3%	3,200	0.2%
CVD: Paroxysmal tachycardia	5,065	0.3%	53	0.4%	5,012	0.3%
CVD: Rheumatic heart diseases	10,852	0.6%	141	1.1%	10,711	0.5%
Diabetes	19,593	1.0%	289	2.4%	19,304	1.0%
Diabetes: Type I	16,900	0.9%	199	1.6%	16,701	0.9%
Diabetes: Type II	5,809	0.3%	166	1.4%	5,643	0.3%
Epilepsy	23,248	1.2%	479	3.9%	22,769	1.2%
Infertility	41,447	2.1%	453	3.7%	40,994	2.1%
Obesity	42,965	2.2%	995	8.2%	41,970	2.1%
Sexually transmitted infection (STI)	101,645	5.2%	1,335	11.0%	100,310	5.1%
STI: Chlamydia	26,163	1.3%	313	2.5%	25,850	1.3%
STI: Herpes viral infection	24,877	1.3%	449	3.7%	24,428	1.2%
STI: Venereal warts	52,997	2.7%	595	4.8%	52,402	2.7%

Table 5.2.1 3. Absolute number of instances of trauma and adverse behaviors

Indicators	Total No. %		Diagnosed with BPD No. %		Not Diagnosed with BPD No %	
Accident	787,952	39.9%	6,895	56.4%	781,057	39.8%
Accident: Fall	500,290	25.4%	4,506	36.7%	495,784	25.3%
Accident: Object enters eye	34,431	1.7%	284	2.3%	34,147	1.7%
Accident: Struck by object	70,457	3.6%	618	5.0%	69,839	3.6%
Death of a close family member	318,391	16.1%	2,937	24.0%	315,454	16.1%
Death of father	183,788	9.3%	1,716	14.0%	182,072	9.3%
Death of mother	89,562	4.5%	899	7.4%	88,663	4.5%
Death of sibling	83,185	4.2%	817	6.7%	82,368	4.2%
Neighborhood deprivation [1]	483,080	25.0%	3,961	33.7%	479,119	24.9%
Poverty [2]	483,081	25.0%	4,652	39.6%	478,429	24.9%
Nonviolent crime (NV)	199,925	10.1%	3,489	28.7%	196,436	10.0%
NV: Petty theft	76,212	3.9%	1,954	16.0%	74,258	3.8%
NV: Fake passports or identification	11,922	0.6%	103	0.8%	11,819	0.6%
NV: Property damage	40,661	2.1%	775	6.4%	39,886	2.0%
Self-harm	80,697	4.1%	6,561	53.6%	74,136	3.8%
Victim of violent crime requiring medical attention (VVC)	68,829	3.5%	2,135	17.5%	66,694	3.4%
VVC: Physical Assault	28,837	1.5%	528	4.3%	28,309	1.4%
VVC: Sexual Assault	6,424	0.3%	742	6.0%	5,682	0.3%
VVC: Abuse	29,838	1.5%	859	7.0%	28,979	1.5%
Violent crime (VC)	68,889	3.5%	1,473	12.0%	67,416	3.4%
VC: Assault	9,758	0.5%	268	2.2%	9,490	0.5%
VC: Threats of violence	16,796	0.9%	565	4.6%	16,231	0.8%
VC: Committing bodily injury	53,417	2.7%	1,017	8.4%	52,400	2.7%

5.2.2 Findings

5.2.2.1 Main Findings

The 5 year cumulative incidences for all analyzed variables were higher in individuals diagnosed with BPD compared to their matched unexposed samples (Figure 5.2.2.1 1). The only exception was for intellectual disability which had no first event instances after date of BPD diagnosis for the exposed and unexposed. The highest rates were for anxiety disorders (Cumulative incidence [95% CI]; BPD 33.13% [31.48. – 34.73%]; not BPD (NBPD) 3.17% [2.98 – 3.79%]), MDD (BPD 25.65% [24.11 – 27.16%]; NBPD 3.04% [2.85 – 3.24%]), and personality disorders (BPD 21.33% [20.26 – 22.39%]; NBPD 0.36% [0.31 – 0.41%]). STIs (BPD 4.64% [4.12 – 5.15%]; NBPD 2.86% [2.74 – 2.99%]) and accidents requiring medical attention (BPD 21.50% [20.13 – 22.64%]; NBPD 10.91% [10.60 – 11.21%]) had the highest cumulative incidences for somatic illnesses and trauma and adverse behaviours category respectively.

Individuals diagnosed with BPD had elevated hazards for all variables included in the main analysis, except for intellectual disability and female infertility (Figure 5.2.2.1 2). Psychiatric disorders had the highest HRs across all of the variables with other personality disorders (HR [95% CI] 67.06 [64.66 – 69.54]) and bipolar disorder (28.18 [27.04 – 29.36]) conferring the strongest relationship. Epilepsy had the largest HR for somatic illnesses (3.38 [3.08 – 3.70]), followed by obesity (2.80 [2.63 – 2.98]). Finally, being a victim of a violent crime (7.45 [7.13 – 7.78]) was the strongest associated traumatic event and self-harm requiring hospitalization had the highest HR for adverse behaviors (17.72 [17.27 – 18.19]).

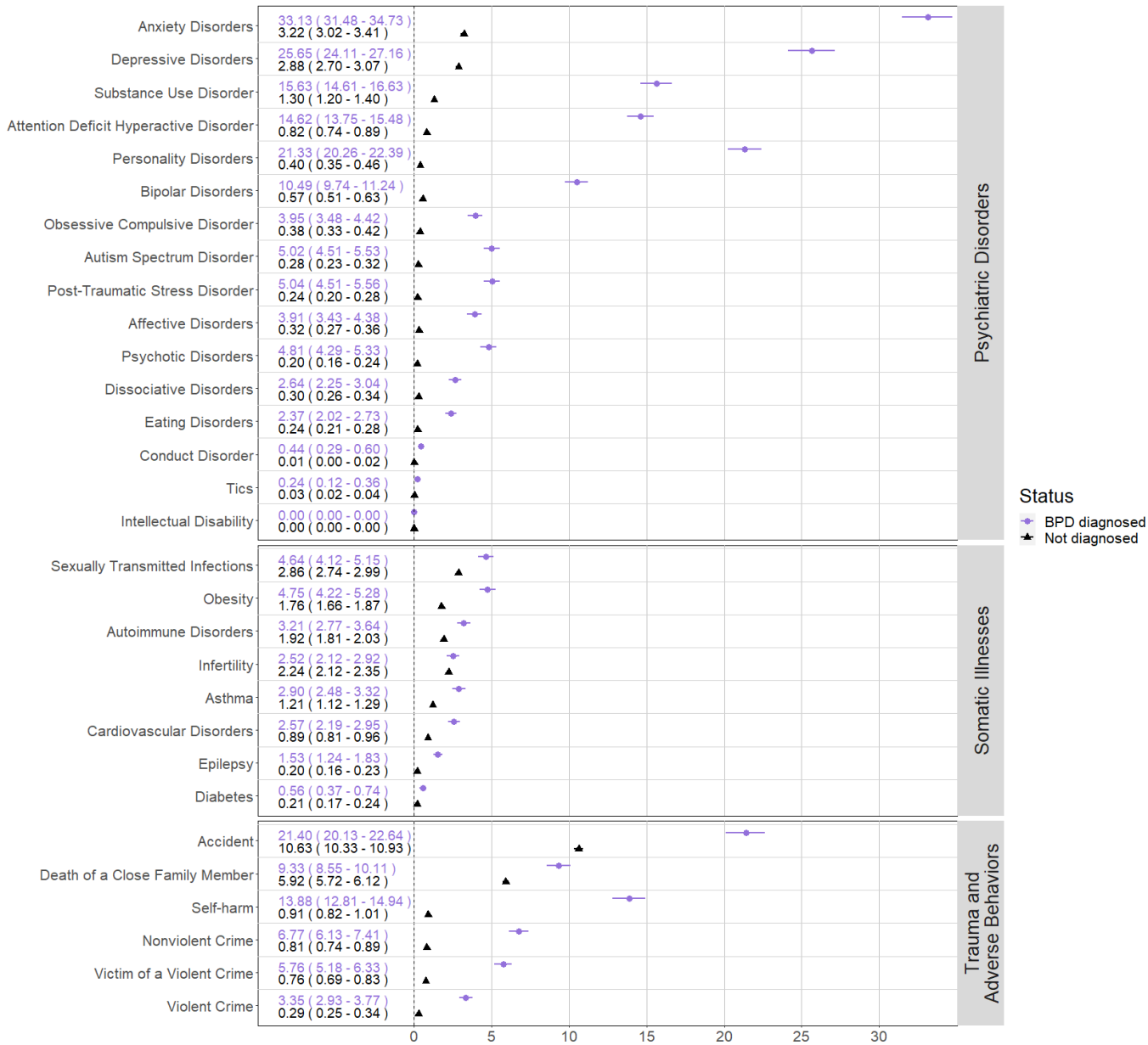

Figure 5.2.2.1 1. Cumulative incidence (95% confidence intervals) by 5 years after borderline personality disorder diagnosis

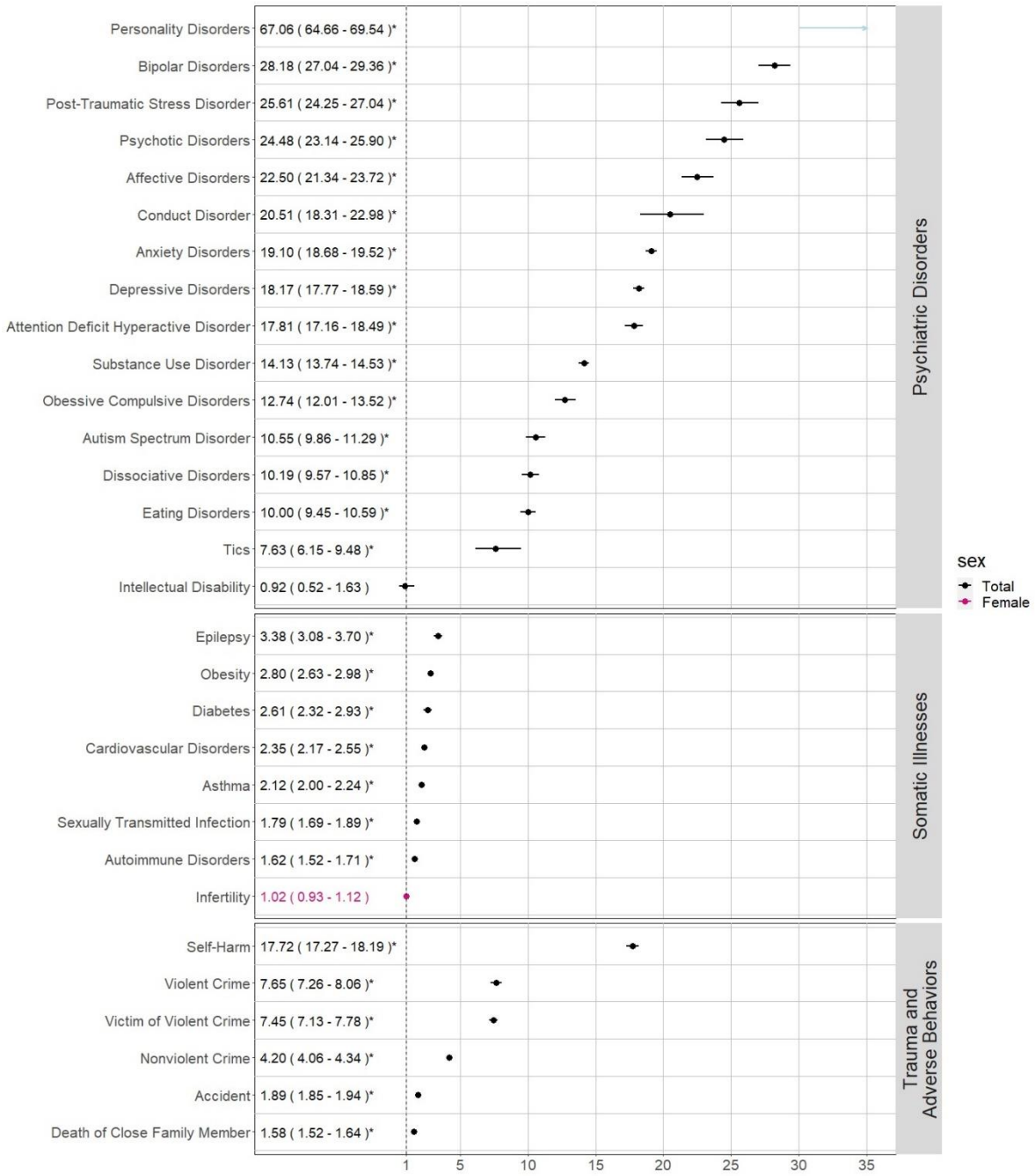

Figure 5.2.2.1 2. Associations with borderline personality disorder (hazard ratio, 95% confidence intervals)

5.2.2.2 Secondary Findings

Through repeating calculation of the cumulative incidence in a sex separated analysis we found that both male and female patients diagnosed with BPD had similar results, and overlapping confidence intervals for most variables. However, female patients diagnosed with BPD had higher cumulative incidences of somatic disorders, e.g., obesity (male 1.80 [0.97 – 2.62];

female 5.29 [4.68 – 5.90]), conversely, male patients had higher values for all adverse behaviors and traumas, e.g., committing a violent crime (male 10.27 [8.14 – 12.35]; female 2.44 [2.06 – 2.83]).

Similarly, the sex separated HRs revealed homogenous values across sexes. However, there were notable exceptions: when compared to females, males had a stronger association with bipolar disorder (male 36.31 [32.62 – 40.41]; female 27.11 [25.93 – 28.33]), PTSD (male 34.99 [29.54 – 41.44], female 24.72 [23.35 – 26.18]), and affective disorders (male 31.42 [27.63 – 35.72]; female 21.32 [20.13 – 22.59]). Females had higher HRs for committing a violent crime (male 6.90 [6.38 – 7.46]; female 8.25 [7.68 – 8.86]), as well as being a victim of a violent crime requiring medical attention (male 5.05 [4.56 – 5.58]; female 8.58 [8.17 – 9.01]).

Through the sibling sex-separated analysis we found that siblings of individuals with a BPD diagnosis were at a higher risk of psychiatric disorders (33 out of 44 total analysis for males and females) and adverse behaviors and trauma (35 out of 42). This effect was not present in somatic disorders (19 out of 36), within which many of the confidence intervals contained 1. Further, individuals with brothers diagnosed with BPD generally had higher HRs compared to those with sisters diagnosed with BPD; although the confidence intervals between brothers and sisters with BPD frequently overlapped. Noteworthy findings include, Antisocial personality disorder (females with a brother diagnosed with BPD (BBPD) HR [95% CI] 10.00 [2.48 – 40.34]; males BBPD 3.01 [0.75 – 12.08]; females with a sister diagnosed with BPD (SBPD) 6.26 [2.94 – 13.36]; males SBPD 3.29 [1.90 – 5.71]), bipolar disorder (females BBPD 6.22 [4.79 – 8.07]; males BBPD 3.80 [2.39 – 6.04]; females SBPD 3.66 [3.18 – 4.22]; males SBPD 3.52 [2.89 – 4.30]), psychotic disorders (females BBPD 4.29 [2.73 – 6.73]; males BBPD 3.59 [2.36 – 5.46]; females SBPD 2.46 [1.92 – 3.15]; males SBPD 2.55 [2.08 – 3.12]), asthma (females BBPD 1.89 [1.51 – 2.37]; males BBPD 1.27 [0.95 – 1.70]; females SBPD 1.46 [1.31 – 1.62]; males SBPD 1.33 [1.19 – 1.48]), death of a close family member (females BBPD 2.24 [1.97 – 2.54]; males BBPD 2.27 [2.00 – 2.58]; females SBPD 1.65 [1.56 – 1.76]; 1.66 [1.56 –

1.76]) , and self – harm (females BBPD 3.46 [2.87 – 4.17]; 2.81 males BBPD [2.27 – 3.49]; females SBPD 2.81 [2.58 – 3.06]; males SBPD 2.04 [1.85 – 2.26])

Additionally, the directional analysis, i.e., treating variables as a risk factor for or outcome following a BPD diagnosis, showed consistent results regardless of temporality. There were a few clear risk factors leading up to a BPD diagnosis: personality disorders (HR [95%CI] risk factor for subsequent BPD diagnosis 71.50 [68.36 – 74.78]; outcome following a BPD diagnosis 43.77 [41.40 – 46.28]), bipolar disorders (risk 35.94 [34.16 – 37.82]; outcome 17.27 [16.12 – 18.51), and psychotic disorders (risk 25.82 [24.19 – 27.56]; outcome 17.96 [16.23 – 19.87]). Epilepsy had a stronger association as an outcome following a BPD diagnosis rather than a risk factor (risk 2.89 [2.59 – 3.22]; outcome 5.36 [4.53 – 6.34]).

5.3 STUDY III

5.3.1 Descriptive Statistics

Out of the included 7,638 participants from CATSS, 12% met our criteria for having mental health problems. The data was broken up into a training (n= 4,554; 51.6% female), tune (n = 804; 50.4% female), and test set (n = 2,280; 51.9% female).

5.3.2 Main Findings

No one model outperformed the other, as the AUC results were similar across each of the model types with overlapping CIs. That said, the two highest performing models were the random forest (AUC [95% CI]: 0.739 [0.708 – 0.769]) and support vector machine (0.735 [0.707 – 0.764]) (Table 5.3.2). The sensitivity and specificity varied between the models, however the positive predictive and negative predictive value were similar. The top most informative variables included parental reported externalizing symptoms, neighborhood deprivation, and information from the national birth register (Figure 5.3.2).

Table 5.3.2. Model performances on the test set

	AUC (95% Confidence interval)	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Logistic Regression	0.700 (0.665 – 0.734)	0.593	0.674	0.192	0.927
XGBoost	0.692 (0.660 – 0.723)	0.835	0.396	0.257	0.906
Random Forest	0.739 (0.708 – 0.769)	0.299	0.913	0.158	0.960
Support Vector Machine	0.736 (0.707-0.765)	0.632	0.701	0.215	0.936
Neural Network	0.705 (0.671-0.737)	0.470	0.792	0.177	0.940

The threshold probability for the majority class was set to 0.50 to generate the results for this table; this means that participants with a probability of having the outcome over 0.50 were classified as having the outcome.

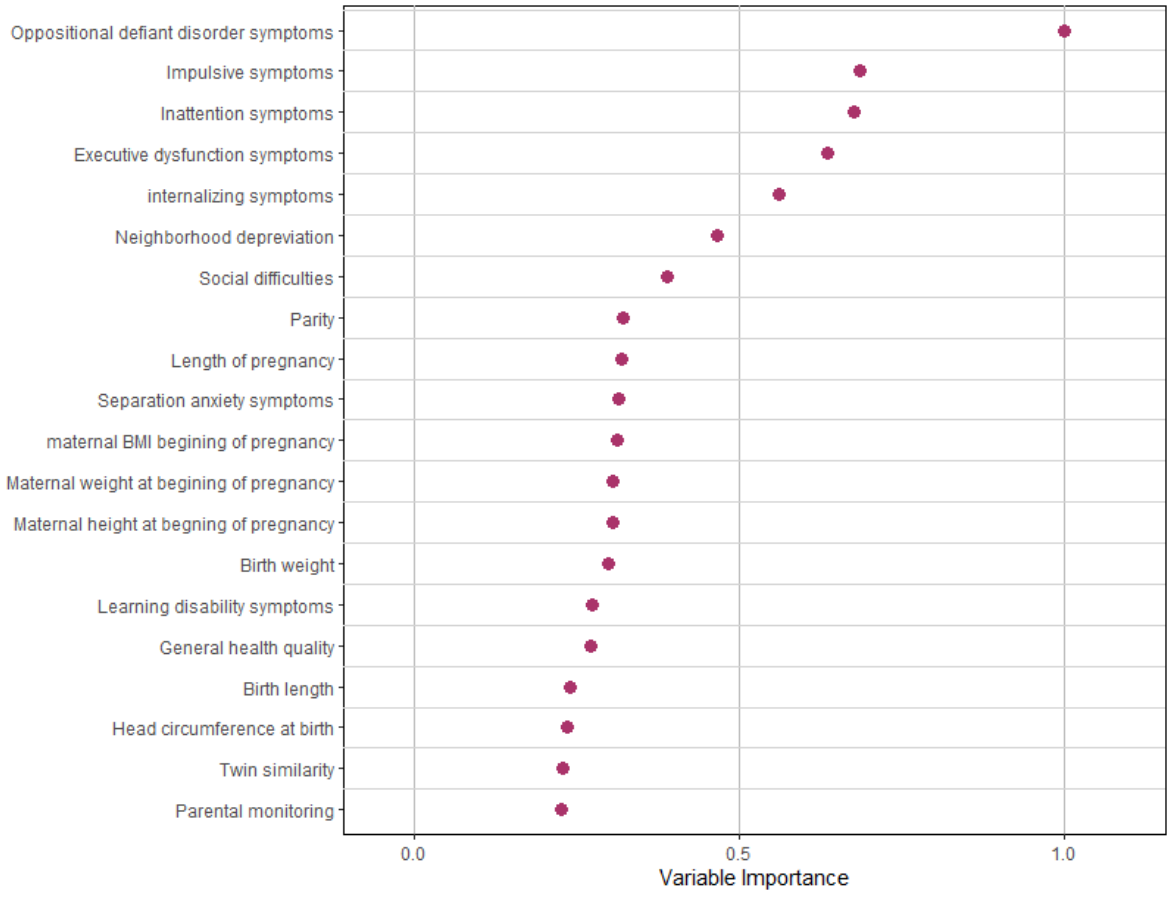

Figure 5.3.2. Scaled variable importance for the top performing variables

5.4 STUDY IV

5.4.1 Descriptive Statistics

A combined total of 8,676 participants from CATSS and NTR were included in the study. The 5,974 participants that were included from CATSS were broken down into a training (N = 4,773), tune (N = 603), and test set (N = 598), while the 2,702 participants from the NTR were kept separate as an external validation set. The four outcome classes aggressive behavior, suicidal behaviors, neither, or both, had imbalanced proportions between CATSS (neither 74.87%, suicidal behaviors 12.93%, aggressive behaviors 7.29%, both 4.63%) and NTR (neither 83.05%, suicidal behaviors 3.15%, aggressive behaviors 12.10%, both 1.70%).

5.4.2 Findings

5.4.2.1 Main Findings

Overall, there was similar performance between the two cohorts, including the model's overall AUC performance (macro AUC [10,000 bootstrap, 95% CI] CATSS test set = 0.709 [0.671 – 0.747]; NTR = 0.685 [0.656 – 0.715] (Table 5.4.2.1). That said, the class performance differed substantially for the suicidal behaviors class between CATSS (AUC 0.713 [0.647– 0.782]) and NTR (0.543 [0.476– 0.611]); the AUC performance in the NTR was no better than chance. The macro sensitivity (test set macro = 0.722; NTR set = 0.683) and specificity (test set macro = 0.584; NTR set = 0.594). The PPV and NPV for both models indicated that the model was correct 30% of the time it placed a participant into any class, and around 80% of the time when it did not place a participant into any class.

The variable importance scores (Figure 5.4.2.1) for the gradient boosted machines and random forest model ranked the predictors consistently. The top performing variables were aggression symptoms at age 15/16, sex, psychiatric symptoms at age 15/16, and polygenic scores related to psychiatric disorders, birthweight, and IQ.

Table 5.4.2.1. Model performances on the test set and external validation set

	AUC (95% CI) [1]	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
CATSS test set					
Macro	0.709 (0.671– 0.747)	0.722	0.584	0.350	0.803
Neither	0.667 (0.619– 0.719)	0.486	0.765	0.862	0.330
Suicidal behaviours	0.713 (0.647– 0.782)	0.470	0.859	0.292	0.929
Aggressive behaviours	0.696 (0.627– 0.767)	0.712	0.604	0.146	0.957
Both	0.759 (0.696– 0.829)	0.935	0.541	0.100	0.994
External validation (NTR) set					
Macro	0.685 (0.656– 0.715)	0.683	0.593	0.303	0.811
Neither	0.715 (0.689– 0.743)	0.784	0.541	0.893	0.339
Suicidal behaviours	0.543 (0.476– 0.611)	0.459	0.654	0.041	0.974
Aggressive behaviours	0.751 (0.724– 0.780)	0.645	0.727	0.246	0.937
Both	0.732 (0.662– 0.807)	0.761	0.600	0.032	0.993

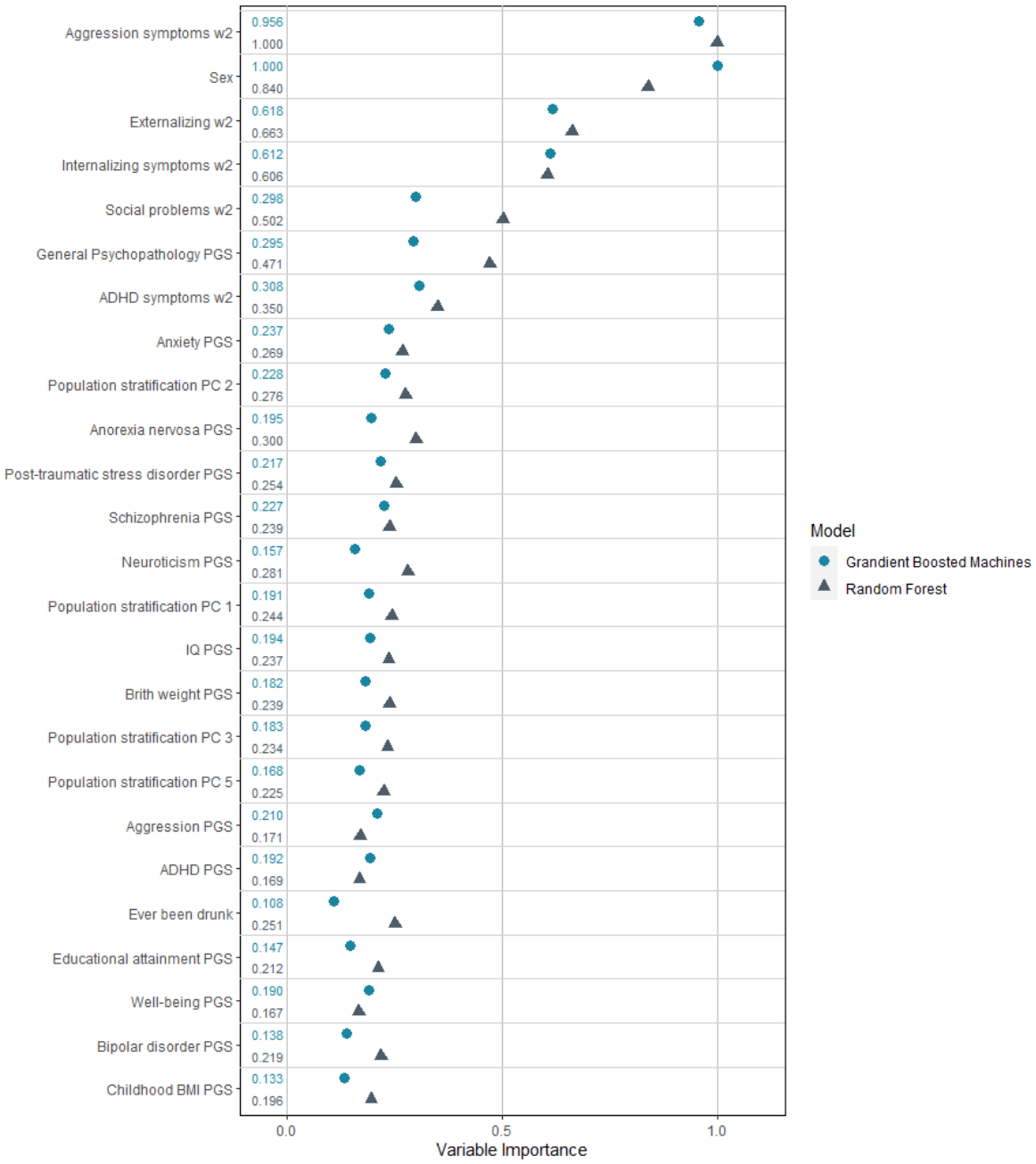

Figure 5.4.2.1. Scaled variable importance for the top 25 scores. *Variable Importance in our model represents the reduction in mean squared error when the variable was split on a node; these values have been scaled for readability. Abbreviations: w2 = Measured at wave 2 (age 15/16); PGS = Polygenic score; PC = Principal component. Gradient Boosted Machines Macro AUC tune set (10 000 bootstrap, 95% CIs): 0.653 (0.606-0.703); Random Forest Macro AUC tune set: 0.628 (0.580-0.678)*

5.4.2.2 Secondary Analysis

Compared to the model in the main analysis, we found lower performance for the model that was created without any genetic variables (macro AUC [10,000 bootstrap, 95% CI] CATSS

test set 0.677 [0.648-0.727]; NTR = 0.682 [0.653-0.710]). That said, the confidence intervals overlapped for the AUCs in the main model and the secondary analysis.

5.5 OVERARCHING RESULTS

In summation, this thesis aimed to first identify the contributions to the development of psychiatric disorders and the outcomes that follow their symptoms and diagnosis; and to utilize these known contributions in prediction models.

5.5.1 Studies I and II

Studies I and II focused on severe psychiatric disorders, BPD and eating disorders, and their comorbidities and other hardships. First, we examined the unique, severe comorbidity of T1D and eating disorders to an extent previously unrealized. We found a modest but positive association between T1D and subsequent eating disorder diagnoses. This finding also carried forward to full siblings of individuals with T1D, but we did not find an association for other family members. Thus, we did not find definitive support for a shared genetic etiology between the two. Second, Study II identified that the markers of BPD are extensive, thus the full context should be taken into consideration when examining individual associations. Additionally, our study identified several novel associations within BPD and their families. Individuals diagnosed with BPD had strong, bidirectional associations with hardships spanning across psychiatric and somatic health, traumatic events, as well as maladaptive behaviors, such as self-harm.

5.5.2 Study III and IV

The second part of this thesis aimed to apply previously identified associations to predict future occurrences of psychiatric symptoms and behaviors. Both models were able to predict the outcomes: general psychiatric symptoms (Study III) as well as aggression, suicidal behaviors, and both (Study IV), better than chance. Although the models did not reach clinical relevance, we obtained valuable information for researchers. In study III, we found that there was no superiority for any one machine learning algorithm, thus logistic regression is still a suitable

approach. The variable importance scores showed that the highest ranking variables were parent-reported externalizing symptoms and register data related to neighborhood deprivation and birth information. Finally, the results from study IV revealed that while polygenic risk scores are not yet clinically relevant on their own, they are informative when used in tandem with other data types, such as questionnaires. Taken together, this thesis places into context the implications of a severe psychiatric disorder, and how this insight may be applied on the path towards precision medicine.

6 DISCUSSION

The results of this thesis provide insight into the physical and psychological comorbidities of severe psychiatric disorders, negative life outcomes, and prediction modeling within psychiatric epidemiology.

6.1 MAIN FINDINGS AND INTERPRETATION

6.1.1 Study I

6.1.1.1 Being diagnosed with type 1 diabetes confers a greater likelihood of receiving an eating disorder diagnosis

In the largest and most thorough study into the comorbidity of T1D and eating disorders to date, we found individuals with a T1D diagnosis had a two-fold risk for a later eating disorder diagnosis. The findings uphold previous studies limited to a smaller sample size or a single country which identified this association [90, 244]. The analyses further examines the association by eating disorder subtype. We found that the "other eating disorder" subtype in our study had the strongest association with T1D. This logically follows, given that withholding insulin to maintain or lose weight is a distinct purging behavior for diabetes patients. However the finding must be interpreted with caution as the confidence intervals overlapped.

6.1.1.2 No consistent evidence for a familial co-aggregation of type 1 diabetes and eating disorders

The results of the familial co-aggregation analyses did not paint a clear picture of the mechanisms behind the association between T1D and eating disorders. Nearly all of the familial co-aggregation analyses had confidence intervals that contained 1, indicating non-statistical significance. However, while there was a positive association between having a full sibling with T1Dand receiving an eating disorder diagnosis in the Swedish sample, the result was not replicated in the Danish sample.

The inconsistent finding for full siblings could be due to population or diagnostic differences between the two countries. Alternatively, the study could be too underpowered to properly

ascertain the effect, indicating that a lack of power could be behind the null findings for the other familial analyses. The results of the Swedish association suggests that environmental factors related to having a T1D diagnosis, e.g., food monitoring and stress, rather than a shared genetic architecture. The increased monitoring of food and eating behavior within the household may contribute to the development of disordered eating behavior in siblings.

To summarize, while our findings for within-individual analyses are robust and fit within literature, less certainty exists for the mechanisms behind this association. The uncertainty is also reflected in literature: An early GWAS of anorexia nervosa found an association with a region that was implicated in autoimmune disorders [117, 245], but this was not replicated in a larger, more recent GWAS [118]. There is evidence to suggest a lack of power, even within our large study of nearly four million persons. Therefore, while we find no evidence in our current study to support a shared genetic architecture between eating disorders and T1D, this may change as sample sizes increase.

6.1.2 Study II

The results from Study II provided insight into the associations of BPD in a detailed, thorough epidemiological approaches. We examined 87 different variables spanning psychiatric disorders, somatic illnesses, trauma and behavior.

6.1.2.1 Borderline personality disorder is associated with extensive psychiatric comorbidities

The results from our study highlight the considerably high magnitude of the association between being diagnosed with BPD and any other psychiatric disorder. BPD diagnosis had high, positive HRs with all psychiatric disorder diagnoses except for intellectual disability. The strongest by far was with other personality disorders (especially antisocial personality disorder), of which individuals diagnosed with BPD had a 67-fold increased risk. This may be a reflection of the diagnostic process, e.g., first diagnosing an individual with personality

disorder unspecified, or misdiagnosis. Thus, a more generalized approach towards diagnosing personality disorders may be warranted [246].

Borderline personality disorder and bipolar disorders

The second highest HRs for individuals diagnosed with BPD was for bipolar disorders. Nearly one quarter of our sample diagnosed with BPD was also diagnosed with bipolar disorder. While this estimate is in accordance to other epidemiological studies, studies using clinical interview data estimate that around 10% of patients with BPD meet the criteria for a concurrent bipolar disorder. As Study II could not assess misdiagnosis rates, we cannot determine the extent of the true comorbidity of these disorders. Previous evidence suggests that BPD is commonly misdiagnosed as a bipolar disorder, especially bipolar type 2, as the mood swings combined with an unstable lifestyle may closely resemble symptoms of hypomania [247, 248]. Some researchers have argued that BPD could be considered as a bipolar spectrum disorder, though this is debated [249].

The directional analysis found that the risk of being diagnosed with BPD *following* a bipolar disorder diagnosis was higher than being diagnosed with BPD *prior to* a bipolar disorder diagnosis. Thus, first being diagnosed with a bipolar disorder may be a common path towards a "final" diagnosis of BPD. Taken into context, clinicians must carefully assess individuals whom they suspect as having a bipolar disorder for BPD symptoms.

Borderline personality disorder, anxiety disorders, and major depressive disorder

It comes as little surprise that the highest cumulative incidences were for depressive disorders and anxiety disorders. These are by far the most commonly diagnosed psychiatric illnesses and previous research has found a high degree of comorbidities between BPD, MDD and anxiety disorders.

Gunderson, et al. [250] found that 90% percent of BPD patients experienced at least one lifetime MDD episode, and 85% had reoccurring episodes. The high degree of comorbidity has

led some researchers and clinicians to question if these disorders are truly independent of each other at an etiological and ontological level [251]. Our results showed an attenuated estimate with only 70% of individuals diagnosed with BPD also receiving a depressive disorder diagnosis in specialist or in-patient care.

BPD patients often meet the criteria for anxiety disorders such as social anxiety or panic disorder. A previous study found that 85% of its BPD sample had met the criteria for anxiety at least once [252], while our results found that 75% of individuals diagnosed with BPD also met the criteria for an anxiety disorder. It is possible that the large degree of comorbidity could indicate an inter-dependent etiology and ontology. BPD patients' hyper sensitivity towards rejection and relationship instability may naturally lead to increased anxiety in social situations [253]. Moreover, the emotional intensity experienced by these patients could indicate an increased liability for panic attacks during moments of heightened anxiety.

Borderline personality disorder and psychotic disorders

Psychotic disorders had one of the highest HRs in our study. This reflects the history of the BPD diagnosis, as "borderline" was initially designated to indicate that patients were on the border of psychosis and neurosis [254]. Nearly a quarter of patients report hallucinations or delusions [1] and full psychotic disorders have been found to present in nearly 40% of patients [255]. We found that 34% of patients diagnosed with BPD were also diagnosed with a psychotic disorder. While the DSM states that psychotic symptoms should be treated as transient, the commonality of long-term psychotic disorders such as schizophrenia may indicate some psychotic symptoms are persistent within a subset of patients. Thus, it may be pertinent to remove the suggestion to treat psychotic symptoms as transient and instead mention psychotic disorders as commonly comorbid.

Borderline personality disorder and post-traumatic stress disorder

Previous research has found extensive associations between a PTSD diagnosis and BPD, and the two disorders share symptoms such as disassociation, depersonalization, and derealization [1, 256]. In line with previous studies, we found that individuals with BPD had a 25-fold increase of being diagnosed with PTSD. However, the absolute numbers were inconsistent with literature. Clinical studies have reported that 30-80% of patients with BPD met the criteria for PTSD, while the results for Study II found an lower estimate of 14.5% [257]. The disconnect could be due in part to a lower number of those diagnosed with either disorder than projected prevalence estimates. Compared to the estimated 5-10%, 0.5% of our entire sample was diagnosed with PTSD, and only 0.6% were diagnosed with BPD compared to the estimated 1.7% [12, 258].

Trauma and, by proxy, PTSD have been cited as an important precursor for the development of BPD [12]. However, literature suggests a bidirectional relationship between PTSD and BPD, leading researchers to hypothesize a cyclical relationship between BPD, trauma, and PTSD [257]. Our findings support said theory; the HRs remained consistent when examining PTSD diagnosis as a precursor and outcome for BPD diagnosis. Thus, the directional associations between PTSD and trauma reflect that this is a deeply coalesced, cyclical association.

6.1.2.2 Somatic comorbidities are common for individuals diagnosed with borderline personality disorder

BPD was found to be positively associated with nearly all of the analyzed somatic conditions. The sole exception is HR for infertility in females, which had a confidence interval that contained 1, indicating non-statistical significance. This falls in line with a Danish study that identified a positive relationship between personality disorders and all somatic conditions [84]. However, their results were attenuated compared to ours, which could indicate that individuals with a BPD diagnosis have a greater risk of somatic comorbidities compared to other

personality disorders. Alternatively, this could be due to population or diagnostic differences within the Danish health care system compared to the Swedish system.

Borderline personality disorder and sexually transmitted infections

STIs had the highest cumulative incidence among the total study sample. Our results support current literature which suggests a link between STIs and a BPD diagnosis, likely arising from increased impulsive sexual activities [259].

Borderline personality disorder and epilepsy

Epilepsy had the highest HR of any somatic illness and 3.9% of individuals with BPD in our sample had comorbid epilepsy diagnosis. Epilepsy is associated with personality disorders as well as personality shifts arising from changes in brain function and damage [22]. The personality shifts, such as Klüver-Bucy syndrome, vary by epilepsy type and can bear a close resemblance to BPD symptoms, e.g., mood swings, increased reactionality, aggression and increased sexual activity. Psychiatric comorbidities, including personality disorders, are common in epilepsy, with rates varying based on epilepsy subtype from 4% in cryptogenic epilepsy to 35% of patients with temporal lobe epilepsy [125]. Study II was the first epidemiological study to report the exact estimate of this comorbidity for individuals with BPD.

Borderline personality disorder, diabetes, and obesity

Obesity and diabetes mellitus (combined type 1 and type 2) had the second and third highest HRs, respectively. Additionally, obesity had the second highest cumulative incidence for individuals diagnosed with BPD. Our results identified that the association between diabetes and BPD was primarily driven by type 2 diabetes. As type 2 diabetes is strongly associated with obesity it is unsurprising that these conditions have similar HRs [92]. Compared to weight-matched individuals, patients with BPD had a higher prevalence of metabolic syndrome, the criteria of which includes type 2 diabetes [124]. While BMI and thus obesity is an imperfect indicator of health, one can argue that in order to receive an obesity diagnosis from a medical doctor one is likely to have health complications surrounding their BMI. Despite the well

documented relationship between obesity and BPD, few, if any studies, have examined the mechanisms behind this association. However, one contributing factor could arise from the use of medication with weight gain as a side effect [260].

The relationship between obesity and BPD is particularly troubling in the light of the social difficulties that accompany both conditions. For example, individuals who are obese receive worse medical care compared to their non-obese counterparts, this could compound with the stigmatization of BPD leading to poor health care by clinicians [261, 262]. Additionally, the stigmatization and bullying victimization associated with obesity could worsen BPD symptoms and/or increase behaviors related to binge eating [263, 264].

6.1.2.3 There is a bidirectional association between borderline personality disorder and trauma

Individuals diagnosed with BPD had higher cumulative incidences and HRs for all trauma related categories. However, the relationship with each variable and BPD diagnosis was bidirectional (with the exception of childhood histories by definition). These findings are consistent with the aforementioned bidirectional relationship with PTSD, and spell a vulnerability towards traumatic events.

Sexual assault had the strongest association with BPD, which fits within what is known about adult victimization and BPD [131]. In particular, emotional dysregulation has been shown to be associated with revictimization of sexual assault [265], thus clinical vigilance for assault victimization of patients with BPD is warranted.

6.1.2.4 Individuals with borderline personality disorder have elevated estimates of adverse behaviors

<u>Borderline personality disorder and crime</u>

In absolute estimates, individuals diagnosed with BPD had higher instances of violent and non-violent offenses. In our sample, 12% of individuals diagnosed with BPD were charged with a violent criminal offense and nearly 30% with a nonviolent criminal offense. Moreover, there

were higher cumulative incidences and HRs for nearly all crime subtypes, with the notable exception of producing or owning a fake passport or other identification. Broken down by crime type, making violent threats had the highest HRs followed by assault and property damage. The cumulative incidences for committing crimes were fairly low, only petty theft and committing bodily injury had cumulative incidences higher than 2%. Thus, our findings fit within literature: Individuals with BPD had an increased likelihood of committing crimes borne out of impulsivity and emotional dysregulation, e.g., threats and assault, rather than planned crimes, e.g., owning fake identification [1, 130]. Our results extend the link between impulsive crimes and BPD to include nonviolent offenses as well.

Borderline personality disorder and self-harm

As repeated self-harm and suicide attempts are core symptoms of BPD, elevated rates were expected for this patient group. Over half of the individuals diagnosed with BPD in our study had an instance of self-harm requiring medical attention, much lower than the previously reported estimates of 90 -- 95% [35]. This disconnect likely arises from differences in measurement, as we only captured severe instances that received medical attention. Furthermore, many cases do not receive medical attention, even if warranted.

6.1.2.5 Broadly, the results were bidirectional and consistent between the sexes

We found similar estimates of the associations between males and females. However, females diagnosed with BPD had higher cumulative incidences of somatic disorders, whereas males with BPD had higher values for adverse behaviors and trauma. More exceptions to this finding include bipolar disorders, PTSD, and personality disorders, for which males had a noticeably higher HR compared to females without overlapping confidence intervals. However, it should be noted that the absolute rates remained higher in females for bipolar disorders and PTSD [134]. This discrepancy is likely due to differences in the baseline rates between males and females in the general population.

When considering the directionality of the associations we found that the associations were largely consistent with the main analyses, which indicates that causality between certain associations, e.g., trauma, may not be as straight forward as initially assumed. The HR for self-harm was higher preceding a BPD diagnosis compared to the HR following a BPD diagnosis. The small attenuation following receiving a diagnosis and likely care appears to be a hopeful trend.

6.1.2.6 Full siblings of individuals with borderline personality disorder had an increased risk of psychiatric disorders, adverse behaviors, and trauma

Through the sibling analysis we found that having a full sibling with BPD conferred an increased risk of psychiatric disorders, adverse behaviors, and traumas but not somatic disorders. As with the main analyses psychiatric disorders had the strongest associations. Siblings of males diagnosed with BPD had higher HRs compared to siblings of females with BPD for the vast majority of analyses. The results must be interpreted with caution as the confidence intervals overlapped for those with brothers and sisters diagnosed with BPD. Nonetheless, the finding insinuates a more severe phenotype for families with males diagnosed with BPD compared to those with females diagnosed. However, we did not find noticeable differences between the estimates of comorbidities between males and females with BPD, suggesting that the symptom severity may indeed be equal. More research is needed to tease apart the sex differences and etiology of BPD.

There was no evidence to support a familial association between BPD and somatic disorders, and there are likely several factors that contribute to the comorbid association within individuals, e.g., subjective experience of the illness. Individuals with BPD symptoms experience more emotional intensity and tend to rate somatic illnesses more severe than objective reports [128]. This means that individuals diagnosed with BPD may seek out treatment more frequently than individuals not diagnosed. Additionally, some illnesses may arise from poor self-care associated with BPD symptoms.

Interestingly, the relationship between the death of a close family member in both individuals with BPD and in their siblings opens the topic of the heritability of early mortality. Siblings of individuals diagnosed with BPD were at a higher risk of having a close relative die. Given that individuals with BPD are at a higher risk for early mortality themselves, it is unsurprising that the strongest association in this category was for a sibling rather than a mother or father. Indeed, for siblings of individuals diagnosed with BPD the HRs for the death of a sibling were twice as high as for the death of a father or mother.

6.1.3 Study III

The performance of the prediction model built in Study III was suitable, but did not reach clinical relevance.

6.1.3.1 No one machine learning technique had superior performance

Study III found that no one machine learning approach had superior performance over the other. A previous systematic review that examined 71 studies similarly found no evidence to support machine learning techniques over standard logistic regression [266]. Thus, the findings uphold the "no free lunch" theory introduced by Wolpurt, which states that there is no "free lunch", i.e., easy decisions for analysis plans, for statisticians as there is no one superior technique [267]. Our study demonstrates this theory to psychiatric epidemiologists in an applied setting. In sum, although machine learning is a current buzzword, researchers from any discipline need not rush to learn the approaches. The decision to implement machine learning techniques in a study can be balanced against the complexity of the data, time needed to learn the desired technique, as well as the overall aim of the study.

6.1.3.2 Externalizing symptoms had the highest variable importance scores

As discussed in section 4.3.3.3, variable importance scores should be interpreted with relative caution. The scores can neither give insight into the direction of the association nor infer causality. That said, the variables with the highest variable importance scores included data

related to externalizing symptoms, neighborhood quality, and data from the maternal birth register.

The top five variable importance scores were externalizing symptoms measured by A-TAC, e.g., oppositional defiant symptoms, impulsivity, inattention, executive dysfunction at age 9 or 12 [171]. These variables are robustly associated with or are symptoms of ADHD, so this finding may reflect the relative stability of ADHD between ages 9 or 12 and 15 [268]. The environmental factors social difficulties and neighborhood quality were also highly ranked, linking neighborhood quality, peer relationships, and psychiatric symptoms in adolescence [57]. For example, peer relationships in childhood are considered to shape self-esteem behavior throughout adolescence, especially in cases of bully victimization, with reports of a cyclical relationship with psychiatric disorders [59, 61].

Finally, factors related to birth and pregnancy, such as the gestational age at birth and parity, had high variable importance scores. Preterm birth has been associated with later social difficulties and psychiatric disorders; and maternal health might be driving this association [269, 270]. Additionally, maternal BMI at the beginning of pregnancy was also implicated, following the literature linking maternal BMI to ADHD symptoms in children [271].

6.1.4 Study IV

6.1.4.1 The model had suitable performance for each class except for the suicidal behaviors class

Study IV sought to create a prediction model which predicted suicidal behaviors and aggression. Given the overlap between the behaviors, we theorized a combined model would streamline assessment within a clinic or population [138]. Our model had acceptable performance and transferred relatively well from the Swedish sample to the Dutch sample. However, the main exception to this finding was the performance of the suicidal behavior class in the Dutch sample. The AUC indicated that performance for this class was no better than chance. This could be due to a number of reasons arising from differences in the population or

measurement, although we found that this was not due to the differences in the year of measurement or of birth years. This most likely cause for this discrepancy were differences in item measurement. The measurement for the NTR contained the following statements, “I deliberately try to hurt or kill myself” and “I think about killing myself”; while CATSS used “Deliberately attempted to injure yourself physically when you were angry or despondent” and “Deliberately attempted to kill yourself when you were angry or despondent”. The differences in the wording likely contributed to the disproportionately poor performance in the self-harm class.

6.1.4.2 Self-reported variables at ages 15 and 16 and biological markers were more informative than parental reported symptoms in childhood

The variable scores do not specify the variables implicated in each specific class, however literature can provide insight into the nature of the association between the variables and each class. Through the variable importance scores, Study IV identified that the best predictors for suicidal behaviors and aggression consisted primarily of self-reported psychiatric symptoms at age 15/16, namely aggression, externalizing and internalizing, and social problems. Biological markers, including sex and genetic variables ranked highly as well.

Self-reported aggression at ages 15 and 16 had the largest variable importance score, which logically follows given that aggression is a fairly stable trait between 15 and 18 [272]. Additionally, sex differences are frequently reported in aggressive and self-harming behaviors [273, 274]. Women are more likely to self-harm and attempt suicide, while men are more likely to die by suicide or exhibit aggressive behavior [37, 274]. The sex breakdown between the classes was consistent with literature, with females being more prevalent in the “both suicidal and aggressive behaviors” class (percentage female: suicidal behaviors = 72.1%, aggressive behaviors = 31.0%, neither 55.2%, both 57.9%). None of the parental reported measures at age 9 or 12 nor the home environment had high variable importance scores. The low ranking of

parental reported symptoms could be due to differences in raters or perhaps a reflection of the instability of many psychiatric symptoms from childhood to adolescence [275].

Genetic scores

The PGS variables and population stratification variables were highly ranked in the model. The general p PGS was ranked the highest, followed by internalizing disorders and externalizing disorders, as well as somatic variables. GWASs for self-harm have had non-statistically significant results and thus little is known about the underlying genetic etiology [276, 277]. However, the PGS for aggression has been well powered and has been reported to have a negative association with BMI, IQ, and birthweight, which were ranked highly in our variable importance scores [278]. Notably the PGS for MDD was not in the top half of the variable importance scores.

The variables used to account for population stratification were in the top half of the variable importance scores as well. These variables were included in order to account for the ancestry information that may cause spurious relationships between a PGS and the sub-populations of the participants [279]. The results indicated that population stratification was indeed useful to include in conjunction with the PGS variables.

6.1.5 Summary

As somatic and psychiatric comorbidities are common within psychiatric disorders [84], Studies I and II sought to further refine this association by focusing on two disorders with the highest mortality rate of any psychiatric disorder: eating disorders and BPD. We found consistent evidence of the association between T1D and eating disorders, but no evidence to support a familial link. BPD is associated with significant stressors and comorbidities throughout many facets of life. Overall, the associations were bidirectional and consistent between the sexes; and, full siblings of individuals with BPD had a greater liability for psychiatric disorders, adverse behavior and trauma but not somatic illnesses. Study III found

that no one machine learning model has superior performance over the over, and externalizing parental-reported variables had the highest variable importance scores. The model created in Study IV had suitable performance in the external data set for all classes except for the suicidal behaviors class. Additionally, externalizing self-report variables and genetic data had high variable importance scores.

6.2 STRENGTHS AND WEAKNESSES

The primary strength of the work presented here is the diversity of the data. The analyses contain data from several national registers, as well as questionnaire and genetic data. Through these data types we were able into gain insights into associations, the etiology behind them, and how these can be applied through prediction modeling. Further, using of national register we had a large enough sample size to examine rare disorders and obtained objective measures by clinicians and other national services. Both the national registers and twin registers contained longitudinal data from our participants, and were thus able to circumvent biases that are present in cross-sectional data, e.g., recall bias. Moreover, our studies contained a combination of study approaches and statistical techniques. With these approaches and techniques, we were able to ask and properly address topics that are of pressing importance to researchers and clinicians.

The major weakness of the studies that relied on national registers was the lack of information on symptoms. Throughout the studies our language has been purposeful; we are looking at individuals *diagnosed* with conditions, not symptoms. This means that disorders that are time intensive to diagnose, such as BPD, and disorders where patients might actively resist treatment, e.g., eating disorders, may go undiagnosed or misdiagnosed. Indeed, we see that in Study II the prevalence of BPD in our sample is nearly half of the estimated world-wide prevalence [12], this indicates that we are likely capturing more severe cases of BPD which could lead to an over estimate of our results. We are also unable to gain insight on symptom

information, which would provide clinicians with better tools for vigilance within their patients across negative outcomes.

The primary weakness for Studies III and IV was the selection bias that may occur from participant drop out in the twin registers. It is likely that participants who drop out have more severe psychiatric symptoms compared to those who responded to multiple waves, which may result in a lack of generalizability in our final results. Additionally, in Study III we may have introduced a bias during the imputation step of the data cleaning process. We performed imputation before the data was split, so information between the sets might have leaked over and caused an inflated estimate of the model performance. Moreover, we also included the outcome as an informative predictor in the imputation step, which may have also created a bias that would lead to an inflated estimate [217]. Finally, for all studies, the results may not be generalizable outside of Northern Europe; although, where applicable, many of our estimates align with current literature.

7 CONCLUSIONS

To conclude, psychiatric disorders are frequently associated with markers across somatic and psychiatric comorbidities, traumatic events, and harmful behaviors. Putting the known associations into a broader context and utilizing them in prediction models helps move psychiatric care into an age of more targeted, personalized medicine. First, we found that individuals with a T1D diagnosis had double the risk of being diagnosed with an eating disorder. However, the etiology behind this association is unclear. Next, we found that a BPD diagnosis was associated with a poorer prognosis across all aspects of life, including psychiatric and somatic health. The results of these studies reflect the need for collaboration between psychiatric clinicians and physicians, and the use of adaptive referrals whenever possible.

In the second part of the thesis, we found that researchers do not need to be concerned with which machine learning method they use. Study III aimed to predict parent reported psychiatric symptoms at age 15 and found that the highest ranked variables were parent reported externalizing symptoms and register data on neighborhood quality and birth. Study IV predicted aggressive and suicidal behavior at age 18 and found that the highest variable importance scores were self-reported measures related to psychiatric disorders as well as psychiatric and somatic genetic variables. The relatively high ranking of the genetic variables shows that prediction models can make use of variables or markers that are not yet clinically informative on their own. Thus, future studies can and should utilize information from a variety of data types and biomarkers for predicting psychiatric disorders or behaviors.

8 POINTS OF PERSPECTIVE

8.1 CLINICAL PERSPECTIVES

8.1.1 Eating Disorder Prevention in Type 1 Diabetes Patients

Individuals with T1D are at a higher risk of being diagnosed with a subsequent eating disorder. We did not find evidence to support an underlying genetic association; optimistically, however, our findings indicate that avenues for prevention are available through diabetes clinics. First, educational programs related to healthy eating behavior and body image should be made readily available to patients with T1D and their caregivers. Additionally, physicians should be aware of the signs and symptoms of early disordered eating behavior in patients, e.g., evidence of insulin restriction or refusal to take medication that may cause weight gain. The routine use of eating disorder screening measures would also help to identify those who exhibit disordered eating behavior [280]. When symptoms are detected by clinicians, referrals for eating disorder care teams should be given; close communication is recommended between the diabetes and eating disorders care teams.

8.1.2 The Expansion of Dimensional Approaches for Personality Disorder Diagnosis

Study II demonstrated the ubiquity of psychiatric comorbidities for patients with BPD. As previously stated, we cannot determine comorbidity from misdiagnosis, but even misdiagnosis can represent a symptom overlap to some extent. That said, certain psychiatric diagnoses were so prevalent in BPD, e.g., MDD, that it may be of more clinical use to add “with mild/moderate/severe features”, e.g., with severe depressive features, to the diagnosis.

However in convergence to the general p, it would be *more* apt to consider a dimensional approach towards psychiatric disorders and personality disorders, as proposed by the Research Domain Criteria [54]. Similarly, the alternative model of personality disorders (AMPD) was included in the DSM-5 as an alternative diagnostic approach to the current binary standard [281]. The AMPD assesses patients in a series of steps with increasing specificity, starting with

global personality functioning and pathological personality traits [246]. The clinician then accesses A or B personality traits and examines for any trait specified disorders, e.g., antisocial personality disorder or BPD. Our results show diffuse symptoms may be the norm rather than the exception, thus a focus on global functioning and domain specific symptoms is prudent. Our findings in conjunction with the general p support the expansion of the AMPD to other psychiatric disorders.

8.2 PRECISION MEDICINE AND MACHINE LEARNING

8.2.1 Future Research Approaches

With the promise that precision medicine driven by machine learning brings, several key points must be considered. As the field develops, a focus on more refined data and model generalizability should be pushed to the forefront. Moreover, it bears repeating that a model is only as accurate as its data, and carries with it all biases and problems with external validity to the model itself [242]. Further, future paths forward should move away from creating new models, and instead focus on improving promising existing models [101]. A shift toward improving existing models would also encourage open, reproducible research, which would further improve the generalizability of the model to new samples.

8.2.2 Clinical Implementation

Care must be taken in the future implementation of prediction models within psychiatric clinics. Namely, the reliance on prediction models could dehumanize the diagnostic process. Clinical supervisors or hospital managers may pressure diagnostic interviews to move faster, which would then limit the clinician-patient bond that grows through careful clinical interviews. A weaker clinician-patient bond may stifle therapeutic success [282]. To combat this, the

subjective patient experience must be incorporated into the diagnostic and treatment process [283].

Moreover, the use of diagnostic models may lead clinicians to distrust their intuitive feelings of the best way to treat or diagnose their patients [283]. No model is perfect, however some individuals may believe that machine based prediction models are nearly infallible [284]. Thus, some patients in particular may be more inclined to trust more in the model's assessment rather than the clinicians'. Clinicians, especially newly in the field, may feel more insecure of their own interpretation and therefore rely more heavily on the model. Clinical training should emphasize the importance of forming conclusions based on all available tests and data.

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"And did you get what
you wanted from this life, even so?
I did.
And what did you want?
To call myself beloved, to feel myself
beloved on the earth."
Late Fragment, Raymond Carver

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