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EDUCATIONAL IMPAIRMENT IN SOCIAL ANXIETY DISORDER AND POST-TRAUMATIC STRESS DISORDER

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INTERFERÈNCIA EDUCATIVA ASSOCIADA AL TRASTORN D'ANSIETAT SOCIAL I AL TRASTORN D'ESTRÉS POSTTRAUMÀTIC

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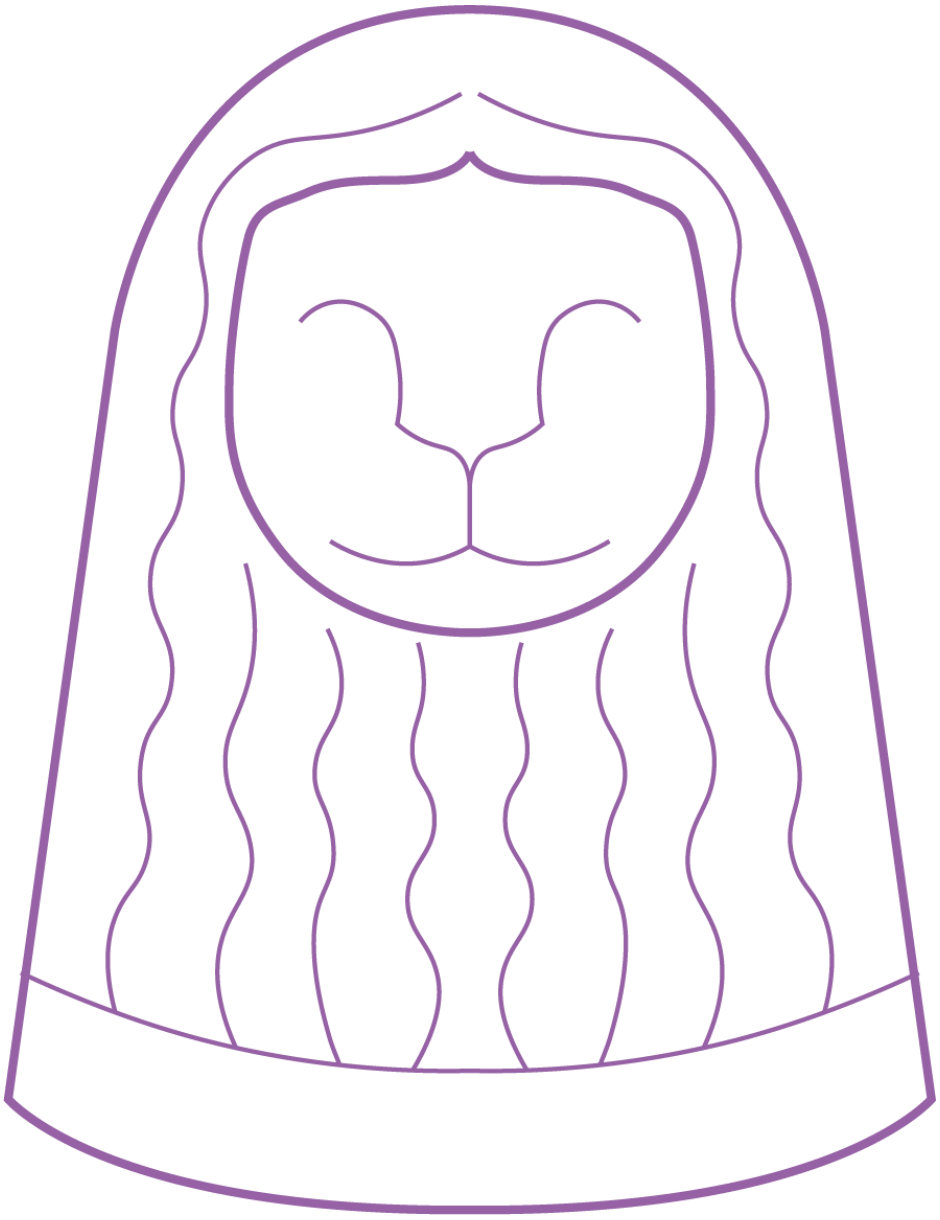
FRAMEWORK



A *Sàlvia*,
que mira si ha corregut terres.

When you reach the end of what you should know,
you will be at the beginning of what you should sense.
Khalil Jilbran

Exiliar l'esguard
Foragitar la pensa
Anomenar aquesta neu abans de pensar-la
Caminar aquesta neu
Com dir-la sense llengua?
El camí que s'endinsa
Claustre de gel
Mots a la deriva
Dir la neu
Desdir-la
Nord, Manuel Bellver

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Andreu, tan lluny, tan prop. Tan esencial.

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PREFACE

This doctoral thesis arises from the interest in investigating whether psychiatric disorders, specifically social anxiety disorder and post-traumatic stress disorder, affect the educational development of individuals.

After completing my undergraduate degree in Psychology, a Masters degree in Psychology, and the 4-year clinical training as a Clinical Psychologist in València, I was awarded two grants by the Alicia Koplowitz Foundation. First, a pre-doctoral training fellowship (2017-2019), followed by a 1-year short-term visiting fellowship (2019-2020). This funding allowed me to move to Stockholm, Sweden for three years and obtain an excellent research training at the Child and Adolescent Psychiatry Research Centre, Department of Clinical Neuroscience, Karolinska Institutet.

As a part of Prof. Mataix-Cols' research team at Karolinska Institutet, I have been able to develop new skills and gain the knowledge I needed to perform the work presented in this thesis. Being affiliated to Karolinska Institutet gave me the opportunity to take advantage of the Swedish nationwide registers and learn about and carry out epidemiological studies.

As a result, during this period, I have been able to publish three manuscripts as a first author, which are thematically related and consititute my doctoral thesis. The sum of the impact factor (IF) of these papers, according to Web of Science Journal Citation Reports™ is 13,553 (2.704 for Study I, 5.813 for Study II, and 5.036 for Study III). I have also published two other manuscripts as a co-author (IF 5.036 and 3.892), which are not included in this thesis.

In my thesis, we first conducted a validation study of the ICD-10 social anxiety disorder code through chart review. Afterwards, we designed two epidemiological studies to explore the association between social anxiety disorder and post-traumatic stress disorder and educational performance by using the large population-based Swedish databases and sound epidemiological methods.

I believe developing this Ph.D. and my life in Sweden during the past 3 years have helped me grow as a student, as a professional, and as a person. I feel I have adquired new skills and improved my knowledge in different areas in order to become a better researcher and a better clinician. I am now more ready than ever to undertake new challenges in my profession.

CONTENTS

ABSTRACT

Background and aims

Psychiatric disorders have generally been linked to academic undearchievement, but previous studies focusing on the association of social anxiety disorder (SAD) and post-traumatic stress disorder (PTSD) and educational outcomes had methodological limitations. Population-based administrative and health registers are often used for research purposes. In this sense, it is important that the diagnostic codes included in these registers are valid and reliable in order to conduct good quality epidemiological studies. This thesis aimed to validate the diagnostic code for SAD – the diagnostic code for PTSD had been previously validated – and, subsequenly, explore the association between SAD and PTSD with objective indicators of educational attainment across the lifespan by using the Swedish population-based registers.

Methods

The ICD-10 code for SAD (F40.1) was validated using chart review methods. Positive predictive values (PPV) and agreement between two raters (using Cohen's kappa) were calculated. Associations between SAD and PTSD and educational outcomes were studied by means of two population-based birth cohort studies of all Swedish individuals born between 1973 and 1997 and followed up until 2013. The exposed individuals were those with registered diagnosis of SAD or PTSD in the National Patient Register. The educational outcomes under study were: elibility to acces upper secondary school, finish upper secondary education, start a university degree, obtain a university degree, and finish postgraduate education. Logistic regression models, adjusted by relevant covariates, tested the association between SAD or PTSD and the educational outcomes.The role of psychiatric comorbidities was also studied. Sibling analyses controlled for familial factors shared by full siblings.

Results

A total of 81% of the reviewed files to validate the code of SAD were considered to be 'true positive' cases (PPV=0.81). Inter-rater agreement regarding the presence or absence of SAD was substantial (κ=0.72). The register-based studies examining the association between SAD and PTSD with educational achievement included cohorts of 2,238,837 and 2,244,193 Swedish-born individuals, respectively. Individuals diagnosed with SAD were less likely to pass all subjects in the last year of compulsory education and less likely to be eligible for a vocational (adjusted odds ratio [aOR]=0.31) or an academic program (aOR=0.52) in upper secondary education, finish upper secondary education (aOR=0.19), start a university degree (aOR=0.47), obtain a university degree (aOR=0.35), and finish postgraduate education (aOR=0.58), compared to unexposed individuals. Similarly, a diagnosis of PTSD was associated with lower odds of achieving each of the assessed educational milestones during the study period, including 82% lower odds of finishing compulsory education (aOR=0.18), 87% lower

odds of finishing upper secondary education (aOR=0.13), 68% lower odds of starting a university degree (aOR=0.32), and 73% lower odds of obtaining a university degree (aOR=0.27). In both epidemiological studies, the results remained largely unchanged when psychiatric comorbidities were taken into account. The sibling analyses showed still statistically significant but attenuated estimates, indicating that part of the observed associations could be explained by factors shared by siblings.

Conclusion

The diagnostic code for SAD in the Swedish National Patient Register is valid and reliable. Individuals with SAD or PTSD, as recorded in this register, are consistently less likely to achieve all educational milestones across the lifespan, over and above a number of confounders such as psychiatric comorbidities and familial factors. Early detection and intervention in these psychiatric disorders is warranted in order to alliviate the long-term adverse effect on academic performance.

RESUM

Introducció i objectius

Tant la Fòbia social (FS) com el Trastorn d'estrès posttraumàtic (TEPT) s'han associat al baix rendiment acadèmic, però els estudis previs presentaven importants limitacions metodològiques. Per a realitzar recerca epidemiològica, és útil utilitzar els registres administratius i de salut poblacionals, com els disponibles a Suècia. Per tal de desenvolupar estudis amb garanties, és important que els codis diagnòstics que contenen aquests registres siguen vàlids i fiables. Aquesta tesi per compendi d'articles té com a primer objectiu validar el codi diagnòstic de l'FS (el codi diagnòstic del TEPT ja ha sigut prèviament validat) per a després explorar, per mitjà dels registres poblacionals suecs, l'associació entre l'FS i el TEPT i els indicadors objectius del rendiment acadèmic al llarg de tot el cicle escolar.

Mètodes

A l'estudi I, el codi diagnòstic de l'FS de la CIM-10 (F40.1) va ser validat per mitjà de la revisió d'històries clíniques i es calcularen el valor predictiu positiu (PPV) i la concordança entre jutges. Els estudis II i III exploraren les associacions entre l'FS i el TEPT i el rendiment acadèmic (respectivament) mitjançant dos estudis observacionals de cohorts poblacionals incloent tots els individus suecs nascuts entre 1973 i 1997, amb informació acadèmica fins a finals de 2013. Els nivells educatius estudiats van ser la idoneïtat per a accedir a l'educació secundària no obligatòria, la finalització de l'educació secundària superior, la iniciació d'estudis universitaris, la finalització d'un grau universitari i la finalització d'estudis de postgrau.
S'analitzaren les dades mitjançant models de regressió logística. També es va estudiar la implicació de les comorbiditats psiquiàtriques en l'associació. Es va dur a terme una comparació entre germans, que permetia controlar els factors familiars compartits. A l'estudi III es van ajustar les anàlisis per la capacitat cognitiva dels individus en una submostra d'homes que havien realitzat el servei militar.

Resultats

El 81% de les històries clíniques revisades per a validar el codi d'FS van ser considerats vertaders positius (PPV = 0,81) i la concordança entre jutges va ser substancial (κ=0.72). Els estudis epidemiològics que examinaren les associacions entre l'FS i el TEPT amb el rendiment acadèmic incloïen cohorts amb 2,238,837 i 2,244,193 persones nascudes a Suècia, respectivament. Les persones diagnosticades amb FS tenien menys probabilitat d'aprovar totes les assignatures en l'últim any d'educació obligatòria (OR ajustada [aOR] amb rang de 0,19 a 0,44) i tenien menys probabilitat de ser idònies per a cursar un programa d'educació secundària superior vocacional (aOR=0.31) o acadèmic (aOR=0.52), menys probabilitat d'acabar l'educació secundària superior (aOR=0.19), menys probabilitat d'iniciar estudis universitaris (aOR=0.47), d'obtenir un grau universitari (aOR=0.35), i d'acabar un post-grau (aOR=0.58), comparat amb persones

no exposades als trastorns. De manera similar, un diagnòstic de TEPT es va associar amb una menor probabilitat de completar tots i cadascun dels nivells educatius estudiats, incloent un 82% menys de probabilitat d'acabar l'educació obligatòria (aOR=0.18), un 87% menys de probabilitat d'acabar l'educació secundària superior (aOR=0.13), un 68% menys de probabilitat d'obtenir un grau universitari (aOR=0.32), i un 73% menys de probabilitat d'obtenir un grau universitari (aOR=0.27). En ambdós estudis epidemiològics, els resultats es van mantenir malgrat excloure les comorbiditats psiquiàtriques. A la comparació entre germans els resultats van romandre significatius però es van atenuar fins a quasi la meitat (rang d'aOR de 0,22 a 0,53) indicant que una part de les associacions observades podria explicar-se pels factors familiars. A l'estudi III, la capacitat cognitiva no va interferir en l'associació.

Conclusió

El codi diagnòstic de l'FS en el registre nacional de pacients de Suècia és vàlid i fiable. Les persones amb FS o TEPT tenen un risc substancialment més gran de disminució del rendiment acadèmic en tots els nivells educatius al llarg de la vida, independentment de factors de confusió com la comorbiditat psiquiàtrica, la capacitat cognitiva general o els factors familiars. Una detecció i intervenció precoç en aquests trastorns psiquiàtrics tenint present esta associació és necessària per a reduir la interferència funcional de les persones que conviuen amb un trastorn psiquiàtric.

LIST OF SCIENTIFIC PAPERS INCLUDED IN THIS THESIS

I. **Vilaplana-Pérez, A**., Isung, J., Krig, S., Vigerland, S., Jolstedt, M., Bjureberg, J., Högström, J., Isomura, K., Rautio, D., Serlachius, E., Rück, C., Mataix-Cols, D., & Fernández de la Cruz, L. (2020). Validity and reliability of social anxiety disorder diagnoses in the Swedish National Patient Register. *BMC Psychiatry*, 20(1), 242. https://doi.org/10.1186/s12888-020-02644-7

II. **Vilaplana-Pérez, A.,** Pérez-Vigil, A., Sidorchuk, A., Brander, G., Isomura, K., Hesselmark, E., Kuja-Halkola, R., Larsson, H., Mataix-Cols, D., & Fernández de la Cruz, L. (2020). Much more than just shyness: the impact of social anxiety disorder on educational performance across the lifespan. *Psychological Medicine*. Advanced online publication 7 January 2020. https://doi.org/10.1017/S0033291719003908

III. **Vilaplana-Pérez, A.,** Sidorchuk, A., Pérez-Vigil, A., Brander, G., Isomura, K., Hesselmark, E., Sevilla-Cermeño, L., Valdimarsdottir, U. A., Song, H., Jangmo, A., Kuja-Halkola, R., D'Onofrio, B., Larsson, H., Garcia-Soriano, G., Mataix-Cols, D., & Fernández de la Cruz, L. (2020). Assessment of posttraumatic stress disorder and educational achievement in Sweden. *JAMA Network Open*, 3(12):e2028477. https://doi.org/10.1001/jamanetworkopen.2020.28477

LIST OF OTHER SCIENTIFIC PAPERS CO-AUTHORED BY THE PH.D. CANDIDATE, NOT INCLUDED IN THIS THESIS

I. García Valls, J. M., Romero Balsalobre, N., **Vilaplana Pérez, A.**, Casas Limones, P., Simarro Quintana, Y., & Serra Sanchís, N. (2007). Respuesta a la TEC en un caso de trastorno explosivo intermitente refractario. *Anales de Psiquiatría*, 23(6), 301-303.

II. Pedrós, A., Andreu, M., **Vilaplana, A.,** Pomares, T., Sorribes, G., Barberán, M., Tomás, A., Tordera, V., & Matínez, P. (2018). Clinical and cognitive insight in patients with psychosis. Is there a relationship? *Schizophrenia Research*, 192, 467–468. https://doi.org/10.1016/j.schres.2017.04.022

III. Andreu Pascual, M., **Vilaplana Pérez, A.**, Pedrós Roselló, A., & Martínez Mollá, P. (2018). Insight, sintomatología y funcionamiento neurocognitivo en pacientes con psicosis. *Revista de la Asociación Española de Neuropsiquiatría*, *38*(134), 491-508. https://dx.doi.org/10.4321/s0211-57352018000200008

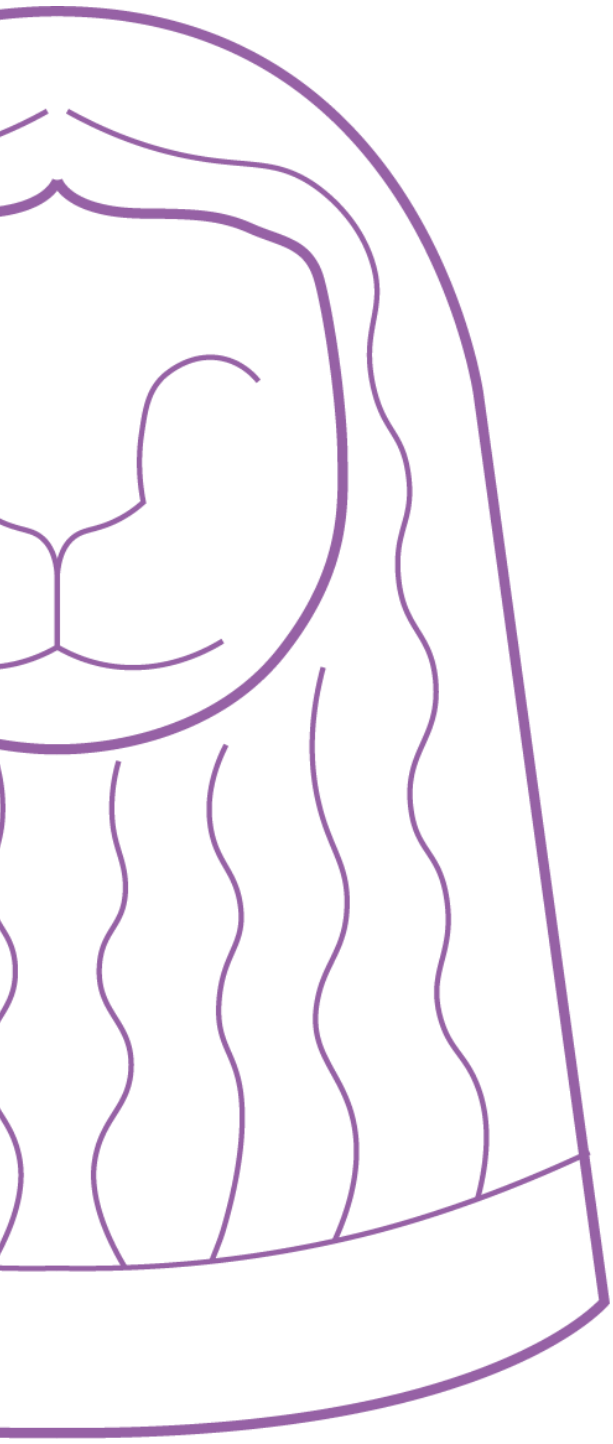
IV. Zhang, T., Sidorchuk, A., Sevilla-Cermeño, L., **Vilaplana-Pérez, A.**, Chang, Z., Larsson, H., Mataix-Cols, D., & Fernández de la Cruz, L. (2019). Association of cesarean delivery with risk of neurodevelopmental and psychiatric disorders in the offspring: A systematic review and meta-analysis. *JAMA Network Open*, *2*(8), e1910236. https://doi.org/10.1001/jamanetworkopen.2019.10236

V. Sevilla-Cermeño, L., Isomura, K., Larsson, H., Åkerstedt, T., **Vilaplana-Pérez, A.**, Lahera, G., Mataix-Cols, D., & Fernández de la Cruz, L. (2020). Insomnia in obsessive-compulsive disorder: A Swedish population-based cohort study. *Journal of Affective Disorders*, *266*, 413–416. https://doi.org/10.1016/j.jad.2020.01.122

LIST OF ABBREVIATIONS

ADHD	Attention-deficit/hyperactivity disorder
ASD	Autism spectrum disorder
CBT	Cognitive behavioural therapy
CI	Confidence interval
CGI-S	Clinical Global Impression – Severity
DALY	Disability adjusted life years
DSM	Diagnostic and Statistical Manual of Mental Disorders
GAF	Global Assessment of Functioning
GDP	Gross Domestic Product
GWAS	Genome-wide association study
ICC	Intra-class correlation
ICD	International Classification of Diseases
ICF	International Classification of Functioning, Disability and Health
κ	Cohen's Kappa
LISA	Longitudinell integrationsdatabas för sjukförsäkrings- och arbetsmarknadsstudier [Longitudinal Integration Database for Health Insurance and Labour Studies]
NPR	National Patient Register
OR	Odds ratio
PPV	Positive predictive value
PTSD	Post-traumatic stress disorder
SAD	Social anxiety disorder
SD	Standard deviation
SNP	Single-nucleotide polymorphism
WHO	World Health Organization
WHODAS	WHO Disability Assessment Scheduled 2.0

1 INTRODUCTION



1.1 PSYCHIATRIC DISORDERS: ANXIETY, TRAUMA, AND STRESS-RELATED DISORDERS

Psychiatric disorders are common, affecting one in six people across countries in the European Union in 2016 (OECD, 2018). The most common psychiatric disorders are anxiety disorders, with a lifetime prevalence as high as 31% (Kessler, Angermeyer, et al., 2007) and an estimated 12-month prevalence of 14% in the European population (or about 69.1 million people) (Wittchen et al., 2011). Living with a psychiatric disorder is highly impairing and presents related societal costs (Druss et al., 2009). In the Global Burden of Disease epidemiological study, psychiatric disorders occupy the fifth place, with affective disorders and stress-related disorders leading the ranking, followed by anxiety disorders (Whiteford et al., 2013).

Although much research on causes, consequences, and treatment of psychiatric disorders is done every year, big gaps of knowledge are yet to be explored. Aiming to shed light into the impairment associated with such disorders, this thesis will focus on the relation between two psychiatric disorders, social anxiety disorder (SAD) and post-traumatic stress disorder (PTSD), and educational attainment across the lifespan. Expanding on the knowledge on education, a crucial area for societal development, these studies have the potential to contribute to the improvement of intervention programmes and policies to help individuals with SAD and PTSD to fulfill their full educational potential in life.

1.1.1 Fear, anxiety, and traumatic events

Fear and anxiety are overlapping but separate emotional adaptative reactions to real or imagined threats and serve to protect us from potentially dangerous situations (Gullone, 2000). Fear is short-lived, its content evolves with age, and disappears rapidly when the threat vanishes; whereas anxiety arises when being faced with imaginary and ambiguous threats, and persists even when the threat is removed (Sylvers, Lilienfeld, & LaPrairie, 2011).

Whereas fear and anxiety are common in everyday life and in many psychiatric conditions, for some individuals, these phenomena can become excessive and persistent, leading to avoidant behaviours and causing substantial impairment (Craske & Stein, 2016). When the threat is overwhelming for almost everyone (World Health Organization, 1993) and menaces the integrity with an expectative of death or injury to the self or others, it constitutes a traumatic event (American Psychiatric Association, 2000). For some individuals, their emotional reaction to a traumatic event may include fear or anxiety (Friedman et al., 2011; Resick & Miller, 2009), but for some others, depending on intrinsic factors, the response will be intense fear, helplessness or even horror (American Psychiatric Association, 2000). Depending on the threat, the vulnerability, and the manifestation of signs and symptoms presented by the individual,

a diagnosis of an anxiety disorder or post-traumatic disorder, among others, may be made.

1.1.2 Anxiety and trauma and stress-related disorders

1.1.2.1 Definition

Both main diagnostic systems, the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases and Related Health Problems (ICD) provide clues to distinguish adaptative, age-appropiate, and evolutive emotional responses – like fear or anxiety – from clinically impairing and persisting manifestations of a psychiatric disorder.

The text revision of the 4th edition of the DSM (DSM-IV-TR) presented a chapter with a broad cluster of disorders which core response was anxiety and avoidant behaviour, including phobias, anxiety disorders, obsessive-compulsive disorder, and stress-related disorders (American Psychiatric Association, 2000). Similarly, the 10th version of the ICD (ICD-10) included a large chapter listing all the neurotic, stress-related, and somatoform disorders (World Health Organization, 1993).

Both these manuals have been recently updated and incorporate substantial changes, with respect to their previous versions. In 2013, when the DSM-5 was released, the anxiety disorders group was splitted and separate chapters were created for the categories of anxiety disorders, obsessive-compulsive and related disorders, and trauma and stress-related disorders (American Psychiatric Association, 2013). In this same vein, the new ICD-11, which was launched in 2018 (and will come into effect in 2022) (World Health Organization, 2018), mostly mimiqued this new classification in separate chapters.

Thus, the group of *anxiety disorders* now contains a cluster of disorders which can be differentiated from each other based on the content and the focus of the individual's specific fears and anxieties. Hence, separation anxiety disorder is characterized by anxiety as a response to the separation from the primary caregiver; in selective mutism, the individual fails to speak in a social situation despite they are able to speak in other contexts; specific phobia is characterized by an irrational fear towards specific situations, animals or objects; in SAD, the anxiety is triggered by a potential negative evaluation by others or the fear of feeling humilated; generalized anxiety disorder comprises an excessive and uncontrollable worry in several areas such as school, family or health; and in agorafobia and panic disorder there are unexpected and recurrent panic attacks with intense physiological and cognitive symptoms that cause distress and fear that may lead to the avoidance of situations or places in which escaping or receiving help is difficult.

As for the group of *trauma and stress-related disorders*, the DSM-5 classification includes five disorders. For the diagnosis of PTSD and acute stress disorder, exposure to a traumatic event is a requirement for the diagnosis. In acute stress disorder, the disturbance lasts between 3 days and 1 month, while if symptoms persist for longer than a month, PTSD would be diagnosed. In adjustment disorder, the individual presents emotional and behavioural symptoms ocurring within 3 months of the ocurrence of a stressor, which is less threatening than a traumatic event. Social neglect or the absence of adequate caregiver during childhood is at the basis of both reactive attachment disorder and disinhibited social engagement disorder; the former is characterized as an internalizing disorder whereas the latter shows a deshinibited and externalizing behavior. Additionally, the ICD-11 has also added the so-called complex PTSD, which describes the condition of individuals who have experienced multiple and sustained traumas from early childhood and have severe functional impairment.

As previously mentioned, anxiety, trauma, and stress-related disorders, as a whole, are very common and prevalent and are associated with significant comorbidity, disability, marked functional impairment, increased rate of medical conditions, and reduced quality of life (Aderka et al., 2012; Stein et al., 2017). Among these disorders, the following sections will focus on SAD and PTSD.

1.1.3 Social anxiety disorder

Human beings are social animals and social relationships (e.g., social support) have allowed us to function and adjust over time to the environmental demands. Socialization cannot be easily avoided on a consistent basis, and some individuals may experience discomfort in relation to the interaction with others (Hofmann & DiBartolo, 2014). When this discomfort becomes excessive, it may trigger a response of high anxiety or lead to consistent avoidance of the situation, which may motivate a diagnosis of SAD.

1.1.3.1 Diagnostic features

SAD, also known as social phobia, is a phobic disorder included in the anxiety disorders cluster since the mid-1960s (Marks & Gelder, 1965). It is characterized by an overwhelming and persistent fear of social situations or performance activities in which the person anticipates a negative scrutiny by others (American Psychiatric Association, 2013). Typical social situations include those involving interacion, observation, and performance, with individuals with SAD being afraid of them. The experienced fear, which must last for at least 6 months for the individual to receive a formal diagnosis, can be either generalized to any social situation (e.g., meeting strangers, talking on meetings or in groups, doing or saying something that will result in humiliation, embarrasement or rejection by others, talking to authority figures, eating or drinking while being observed, going to school or shopping) or restricted to a specific social

situation such as public speaking, constituting a subtype of the disorder (National Guidance Alliance, 2013).

After the situation triggers the fear, hyper-arousal symptoms such as blushing, sweating, trembling or stuttering are the common expression of this disorder, and the behavioural tendency is to completely avoid the feared social situations, or endure them but under great distress (American Psychiatric Association, 2013). In children, the disorder can manifest as mutism in social situations or avoiding going to school. They can also behave with irritability, shyness or overly reliant on their parents (National Guidance Alliance, 2013).

1.1.3.2 Prevalence and course

Lifetime prevalence of SAD has been established to be approximately 4% of the worldwide general population, although the estimates reach up to 8-12% in some countries (Lijster et al., 2017; Ruscio et al., 2008). The 12-month prevalence is estimated to be 2.4% (Stein et al., 2017). These percentages translate into more than 10 million of European citizens presenting with SAD (Wittchen et al., 2011).
SAD is more frequent in women, with a 2:1 ratio (Wittchen et al., 2011), and its mean age of onset is during the adolescence, around age 14 (Lijster et al., 2017). It also has a tendency to be persistent and chronic if left untreated (Steinert, Hofmann, Leichsenring, & Kruse, 2013).

1.1.3.3 Comorbidities

SAD has a remarkably high degree of comorbid conditions, with up to 80% of all SAD cases fulfilling lifetime diagnostic criteria for at least one other psychiatric disorder (Fehm, Pelissolo, Furmark, & Wittchen, 2005; Katzman et al., 2014; B. D. Stein et al., 2017). The most commonly comorbid disorders are other anxiety disorders, substance use disorder, body dysmorphic disorder, impulse control disorder, and major depressive disorder (Ohayon & Schatzberg, 2010; Ruscio et al., 2008; Stein et al., 2017). Also, SAD has been associated with an increased risk of suicidality and suicide attempts, compared with those without SAD (Katzelnick & Greist, 2001; Stein & Kean, 2000).

1.1.3.4 Aetiology and risk factors

While much is known about the clinical features of SAD, there are important gaps in our understanding of its aetiology (Craske & Stein, 2016). As with many psychiatric disorders, the development of SAD follows a diathesis-stress model (Barlow, 2004), which suggests that pre-existing vulnerability factors (e.g., genetics and intrinsic vulnerabilities) interact with distal and proximal environmental factors (e.g., peer victimization or parental style) for its development (Gazelle & Rubin, 2019; Spence & Rapee, 2016).

SAD is considered a familial disorder. Family studies suggest that the odds of developing SAD for first-degree relatives of individuals with the disorder are around five times higher than for those that do not have relatives with SAD (Isomura et al., 2015). Further, this risk attenuates when genetic relatedness decreases, as first-degree relatives of individuals with SAD (50% genetic similarity) have a significantly higher risk of having SAD than second-degree relatives (25% genetic similarity), and third-degree relatives (12.5% genetic similarity) (Isomura et al., 2015). Indeed, evidence from twin-studies shows that the contribution of genetic factors is relevant, with meta-analytic estimates of 0.41 for the genetic share (Scaini, Belotti, & Ogliari, 2014). The first genome wide-association study (GWAS) in SAD confirms a genetic basis for the disorder (Stein et al., 2017).

With regards to environmental factors, meta-analytic evidence concludes that the contribution of non-shared environmental factors is 0.54 (Scaini et al., 2014). Individual experiences that have shown to contribute to the non-shared environment include traumatic experiencies, like early physical and sexual trauma (Erwin, Heimberg, Marx, & Franklin, 2006; Fullana et al., 2020). Negative school experiences, extra-curricular activities or peer relationships may also be particularly important in the aetiology of SAD (Norton & Abbott, 2017; Spence & Rapee, 2016). As for shared environmental influences, an over-controlling and over-protective style of parenting have also been mentioned as potentially important in the development of SAD (Norton & Abbott, 2017). However, shared environmental factors seem to make a small or negligible contribution to the aetiology of the disorder (Isomura et al., 2015; Scaini et al., 2014).

Neurobiological research has pointed to a hyperactivation of the fear circuit involving the amygdala, insula, hippocampus, and orbital frontal regions of the brain (Brühl, Delsignore, Komossa, & Weidt, 2014; Fox & Kalin, 2014), in addition to a deviated serotonin and oxcitocin regulation (Stein & Andrews, 2015; Ziegler et al., 2015), as the most likely systems involved in SAD. Moreover, SAD is also associated with behavioural withdrawal (Leichsenring & Leweke, 2017) and with the presence of behavioural inhibition (i.e., wariness when exposed to novel situations) (Kagan, Reznick, Clarke, Snidman, & Garcia-Coll, 1984). A recent study found that 15% of toddlers and children present the most severe form of behavioural inhibition and it has been associated with a seven-fold risk of developing SAD later in life (Clauss & Blackford, 2012). Additionally, dysthymia, major depression, and neuroticism also have shown highly suggestive evidence as risk factors for SAD (Fullana et al., 2020).

1.1.3.5 Treatment

According to treatment guidelines, the treatment for SAD can include psychological, pharmacological interventions or a combination of both (Pilling et al., 2013). Cognitive behavior therapy (CBT) and selective serotonin-reuptake inhibitors (SSRIs) are the

evidence-based interventions (Katzman et al., 2014; National Guidance Alliance, 2013). For the short-term treatment of SAD, CBT and SSRIs appear to have similar efficacy (Canton, Scott, & Glue, 2012), but CBT effects seem to be longer-lasting (Davidson et al., 2004). For patients for whom psychotherapy is too terrifying at first (because of the exposure to feared situations), more immediate improvements are achieved with pharmacotherapy, until anxiety has been reduced and psychotherapy becomes a more acceptable option (Leichsenring & Leweke, 2017). Nonetheless, CBT is less invasive than pharmacotherapy and has less side effects and, thus, should be considered as first-line of treatment, according to current treatment guidelines (National Guidance Alliance, 2013). Besides CBT, which has showed larger effects on the outcomes and superiority to the other approaches, psychodynamic psychotherapy, interpersonal psychotherapy, mindfulness, and supportive therapy have also shown some efficacy for the treatment of SAD (Mayo-Wilson et al., 2014; Salzer et al., 2018). Internet-delivered CBT for SAD, which facilitates a broader access to CBT, has shown good results in young people and adults with the disorder (Hedman et al., 2011; Nordh et al., 2017).

1.1.4 Post-traumatic stress disorder

Being exposed to traumatic events is relatively common in the general population. For example, 70% of 68,894 adult respondents to the World Mental Health Survey across six continents reported being exposed to at least one of 29 potentially traumatic event types (Benjet et al., 2016). The type of traumatic events generally vary by sex, with men being more frequently exposed to physical assault and combat and women to rape and sexual assault. Early traumatic experiences are found to be a general risk factor for several mental disorders, including SAD (Norton & Abbott, 2017), but also other anxiety disorders (Blanco et al., 2014), affective disorders (Bortolato et al., 2017; Köhler et al., 2018), and psychotic disorders (Belbasis et al., 2018; Radua et al., 2018), with percentages of individuals with severe mental illness previously exposed to traumatic events ranging from 49% to 100% (Grubaugh, Zinzow, Paul, Egede, & Frueh, 2011). Nevertheless, PTSD is still the most prevalent psychopathological consequence of exposure to traumatic events (Shalev et al., 2019).

1.1.4.1 Diagnostic features

PTSD is a psychiatric condition that may develop after exposure to a threatening or horrifying traumatic experience (e.g., a serious accident, physical and sexual assault, abuse, war or torture) (National Guideline Alliance, 2018). PTSD includes four symptom clusters: re-experiencing (nightmares, flashbacks), persistent avoidance (behavioural and cognitive), negative alterations in cognition and mood (e.g., inability to recall important aspects of the trauma, anhedonia, negative beliefs and emotions of self or others, elevated self-blame, a negative emotional state, and reckless or self-destructive behavior), and increased arousal and reactivity (e.g., irritability, agitation, anger, hypervigilance, problems with concentration, sleep disturbance). When

emotional numbing and dissociation are present (despersonalization or derealization), this should be specified (American Psychiatric Association, 2013), since this will have implications in the treatment.

Usually, symptoms are developed within the first month after the exposure to the event, although they can appear even after 6 months (in less than 15% of PTSD cases) (National Guideline Alliance, 2018), which is considered PTSD with a delayed expression (American Psychiatric Association, 2013).

A diagnosis of a subtype of PTSD for children younger than 6 years of age can be made when, instead of complaining of re-experiencing or avoidance in a direct manner, the traumatic event reappears in nightmares or repetitive trauma-related play; intrusive thoughts and avoiding things related to the event are present and there are increased behavioural difficulties, problems concentrating, and hipervigilance, which last for more than a month (National Guideline Alliance, 2018).

1.1.4.2 Prevalence and course

Despite the high probability of being exposed to a traumatic event (Benjet et al., 2016) and taking into account that, after the exposure, approximately a third of the individuals exposed will develop PTSD (American Psychiatric Association, 2013), it is important to note that most individuals exposed to trauma are resilient and can recover from it (Bonanno, 2004). The prevalence of PTSD is directly related to the severity and type of traumatic event, with torture, rape or direct combat conferring a very high risk (Kessler et al., 2017). The worldwide lifetime prevalence of PTSD is 5.6% among those individuals exposed to trauma and 3.9% of the general population (Koenen et al., 2017). However, the prevalence varies by country, ranging from 0.5% to 14.5% across countries (Koenen et al., 2017), and by age. For example, the 12-month prevalence across the European Union has shown to decline by age range, with 14-34 year olds having a prevalence of 2.9%, 35–65 year olds of 1.3%, and those older than 65 years of 1.1% (Wittchen et al., 2011). Lifetime risk in women is twice that in men (Yehuda et al., 2015).

PTSD onset occurs later in life than other anxiety and mood disorders (Kessler, Amminger, et al., 2007), with a mean age of onset of 26.6 years (Lijster et al., 2017). There is a wide variation across countries and income groups, with an age of onset of around 25-28 years in high income countries, compared with low-middle income countries, where the mean age is around 43 years (Koenen et al., 2017).

1.1.4.3 Comorbidities

An estimated 75%-80% of individuals with PTSD exhibit psychiatric comorbidity, especially substance use disorders, affective disorders, and anxiety disorders (American Psychiatric Association, 2013; Pietrzak, Goldstein, Southwick, & Grant, 2011).

Additionally, individuals with PTSD have higher rates of suicide attempts and deaths by suicide, with odds up to 13 times higher, compared to those without PTSD (Gradus, 2018; Gradus et al., 2015).

1.1.4.4 Aetiology and risk factors

PTSD responds to an interaction between a pre-trauma, peri-trauma, and post-trauma risk factors. Although the mechanisms leading to PTSD are yet to be fully elucidated, the main risk factors are related to genetic susceptibility, the type of traumatic event, the individual responses, and the social context (Auxemery, 2012).

Research has found that the genetic contribution to PTSD is complex, since genetic factors can influence both the exposure to traumatic events (e.g., higher likelihood to participate in combat or violent situations) and the vulnerability to develop the disorder following a traumatic event (Afifi, Asmundson, Taylor, & Jang, 2010; Lebois, Wolff, & Ressler, 2016). Twin studies estimate the heritability of the genetic vulnerability at 49% (Kremen, Koenen, Afari, & Lyons, 2012; Wolf et al., 2018). GWAS studies have shown a polygenic risk for PTSD (Gelernter et al., 2019; Nievergelt et al., 2019). Of note, PTSD shares high genetic correlations with other psychiatric disorders, particularly major depressive disorder and schizophrenia (Nievergelt et al., 2019).

Some biological features of PTSD reflect vulnerability factors (e.g., hearth-rate variability, abnormally large cavum septum pellucidum or smaller hyppocampus) (Pitman et al., 2012; Shalev, Liberzon, & Marmar, 2017), whereas some neuroendocrine factors seem to represent trauma-induced alterations. After traumatic exposures, sympathetic nervous system and the hypothalamic–pituitary–adrenal (HPA) axis are activated by the stress response, releasing glucocorticoids and catecholamines. This activation leads, through a negative feedback inhibition of the HPA axis, to an immune disturbance and a neuroinflammatory response (Xue-Rong, Qian-Bo, Kai, Kun-Ming, & Zhi-Jie, 2018).

Regarding environmental factors, some sociodemographic factors such as being a woman, being from certain ethic groups (i.e., indigenous people from the Americas) or low socioeconomic status have received evidence as risk factors for PTSD. Regarding pre-trauma factors, having a history of somatic diseases, family history of psychiatric disorders, being a victim of adversity during childhood or childhood abuse (Tortella-Feliu et al., 2019) also have shown suggestive evidence.
Morever, and because PTSD is conditional to trauma exposure (Benjet et al., 2016), peritrauma factors such as higher severity of the experienced traumatic event (e.g., torture, being trapped during an earthquake, mass violence) and cumulative exposure to traumatic events (e.g., individuals exposed to mass conflict), have also shown suggestive evidence of increasing the risk for PTSD. Post-trauma variables have shown

less impact on the risk of developing PTSD, compared to pre- or peri-trauma factors (Tortella-Feliu et al., 2019).

1.1.4.5 Treatment

Following the treatment guidelines for PTSD, clinical judgment and patient preferences, as well as patient response to previous psychotherapy or pharmacotherapy, are all important factors in designing the treatment approach for PTSD (Guideline Development Panel for the Treatment of PTSD in Adults, 2019).

As for psychotherapy, CBT is considered an effective first-line option. Trauma-focused CBT, prolonged exposure therapy, and cognitive therapy for PTSD have also empirical support (Katzman et al., 2014; National Guideline Alliance, 2018).
Eye-movement desensitization and reprocessing (EMDR), narrative exposure therapy, and brief eclectic therapy can be effective in some instances but are recommended conditionally (Guideline Development Panel for the Treatment of PTSD in Adults, 2019). For example, EMDR can be offered to adults with PTSD who have presented symptoms for more than 3 months after a non-combat-related trauma (National Guideline Alliance, 2018). Regarding Internet-delivered CBT and virtual reality exposure, both have demonstrated efficacy, specially when the patient presents low risk of self-harm (National Guideline Alliance, 2018).

Of note, the widespread use of early interventions (i.e., psychological debriefing) after being exposed to a traumatic experiences in order to prevent PTSD is not recommended since they may increase the risk of developing PTSD (National Guideline Alliance, 2018). Rather, screening, assessment, and treating appropiated individuals is preferred (Katzman et al., 2014; National Guideline Alliance, 2018).

Pharmacological interventions with good evidence of efficacy in treating PTSD are mainly antidepressants (SSRIs and serotonin-norepinephrine reuptake inhibitors [SNRSs]), including fluoxetine, paroxetine, sertraline, and venlafaxine (Katzman et al., 2014; National Guideline Alliance, 2018). Research evaluating combined psychological and pharmacological treatments in PTSD is limited and requires further study (Katzman et al., 2014).

1.2 FUNCTIONALITY: ADAPTATION AND IMPAIRMENT

Adaptative functioning refers to the set of skills required to live an independent and self-governing life (American Psychiatric Association, 2013). Limitation in adaptative functioning hinders the achievement of age-appropriate standards of behaviour and the ability to live successfully. When assessing psychopathology and clinical significance in psychiatric disorders, two main components are key: distress and functional impairment. While distress refers to the experience of symptoms by the individuals themselves, functional impairment defines the deficits appearing in multiple life

domains of the individual, which are independent from the symptoms of the disorders (Ustün & Kennedy, 2009). In fact, impairment in functioning may have a greater impact in the quality of life than the clinical symptoms (Aderka et al., 2012) or can appear before the symptomatology of the disorder manifests (Winters, Collett, & Myers, 2005), highlighting the importance of considering impairment separately in the assessment, classification, and treatment of psychiatric disorders.

In this line, a framework to assess the functional impact of individuals across all areas in life, besides the description and classification of symptoms and disorders, is essential for guiding clinical-decision processes. In an attempt to meet this need, the World Health Organization (WHO) launched the International Classification of Functioning, Disability and Health (ICF) (World Health Organization, 2001), a biopsychosocial standard for the measurement of the impairment in 47 domains, such as social interactions or school functioning. Moreover, the DSM-5 (American Psychiatric Association, 2013) has replaced the Global Assessment of Functioning (GAF), a largely used scale but with limitations, by the WHO Disability Assessment Scheduled 2.0 (WHODAS) (Ustün et al., 2010). The WHODAS' framework is also based on the conceptual framework of the ICF, and focuses in six major areas of functioning, namely cognition, self-care, mobility, social interactions, life activities, and participation in society.

Promoting the prevention and intervention on functional impairment could help to improve societies efficiency in general. A paramount consequence of the impairment related to psychiatric disorders is their economic burden, which is estimated at up to 4% of the Gross Domestic Product (GDP) – or over EUR 600 billion – across 28 European Union countries in 2015, as a direct cost of health system services and social security benefits (OECD, 2018). Additionally, there are a series of indirect costs, such as those related to the caregivers, that also add to the cost of illness, which are disproportionally high in psychiatric disorders compared to the direct and indirect costs for somatic disorders (Wittchen et al., 2011). Furthermore, the opportunity costs associated with having poorer educational and work outcomes, with lower employment rates for people with psychiatric disorders and reduced productivity due to higher absenteeism and presenteeism, added up to over EUR 240 billion or 1.6% of GDP across countries in the European Union in 2015 (OECD, 2018). Moreover, psychiatric disorders in the European Union in the same year also lead to premature mortality: over 84,000 people died of associated consequences and suicide. Early mortality contributes to the disability adjusted life years (DALY) index, since DALYs are based on years of life lost from premature death and years of life lived in less than full health. One DALY can be thought of as one lost year of healthy, free of disease, and disability life (Murray et al., 2013). In terms of DALY, depression became by far the most burdensome disorder of all diseases in Europe, especially for women. PTSD is also worth

mentioning since appears in the ranking of most burdensome disorders (of DALY estimates) in European individuals older than 15 years old (Wittchen et al., 2011).

This illustrates the importance for health-care systems to work in a collaborative manner with social and educational services. Taking into consideration the above figures, patient interventions should go beyond the treatment of the psychiatric symptoms, and also take into account the functional impairment associated to them. Helping individuals through intervention plans aiming to decrease their functional impairment would increase their quality of life and also contain the impact on the economy and societies growth. Since this thesis will focus on the educational impairment associated to SAD and PTSD, we will now describe the overall funcional impairment specifically associated to these disorders.

1.2.1 Functional impairment in SAD and PTSD

Impairment related to SAD is high, with more than 90% of individuals with the disorder reporting psychosocial impairment (Leichsenring & Leweke, 2017). There is a linear association between the severity of the disorder (e.g., number of situations affected by social fears) and diverse indicators of impairment (Fehm et al., 2005; Stein & Kean, 2000), especially in mental health, social, educational, and ocupational areas, rather than home and family domains, where the individuals with SAD appear less impaired (Aderka et al., 2012; B. D. Stein et al., 2017).

The social domain is the most affected, since individuals with SAD usually face exclusion from peer interactions and have fewer friends (Gazelle & Rubin, 2019). Related to their fewer social interactions, it is common that students with SAD refuse or drop out of school prematurely, specially when social demands increase in the clasroom (Van Ameringen, Mancini, & Farvolden, 2003). Additionally, a lower level of education affects employment rate, and being unemployed is a firm predictor for the persistence of SAD (American Psychiatric Association, 2016). Individuals with SAD are usually less productive at work and commonly face underpayment (Alonso et al., 2004; Stein & Kean, 2000), which in the long run can translate into higher rates of financial dependency (Katzelnick & Greist, 2001).

In a similar way, PTSD has also been associated with high levels of impairment across all domains of functioning, comprising mental and physical health, social and familial relationships, educational, and ocupational functioning (Olatunji, Cisler, & Tolin, 2007). Although we have mentioned the high degree of impairment associated to SAD, the burden of PTSD seems to be even greater (Aderka et al., 2012; Olatunji et al., 2007), comprising affectation in relationships and family functioning (Birkley, Eckhardt, & Dykstra, 2016). PTSD is associated with work-related disabilities, including significant rates of sickness absence, reduced work performance or complete failure to return to work after trauma exposure (Wald & Taylor, 2009). It also impacts

the physical health of the sufferers (Olatunji et al., 2007), including cardiovascular diseases or life threatening infections (Fang et al., 2019; Song et al., 2019) and their associated health care expenses (Pietrzak et al., 2011).

Below, we will specifically focus on the educational attainment of individuals with SAD and PTSD.

1.2.1.1 Educational attainment in SAD and in PTSD

Education has a great influence in healthy societies and it is considered a universal free fundamental right (UN, 1948). The level of education acquired by the population is associated with a country's ability to increase its standard of living, compete in global markets, promote participation in civic affairs, and reduce street crime (Lochner, 2004; OECD, 2001). Educational attainment is also considered a leading social determinant of health (Braveman & Gottlieb, 2014) and has a relevant role in economic disparities, social engagement, employment stability, and life expectancy. Every action for preventing school drop outs and academic failure contributes to prevent major social, health, labour, and economic implications (Belfield, 2007).

- <u>SAD and educational attainment</u>

School performance in SAD can be negatively affected by conditions like fear of giving presentations and hesitation to ask the teacher for help, as well as influenced by the high absenteeism (Beidel et al., 1999). Previous research has shown an association between the disorder and educational impairment, school dropout, and poor work performance (Brunello et al., 2000). For example, the Epidemiologic Catchment Area study reported that adults with SAD or with subthreshold SAD, compared to controls of the same age without the disorder, presented significant differences in three retrospectively self-reported school performance measures, including poor grades, repeating grades, and expulsion from school (Davidson, Hughes, George, & Blazer, 1994). The Ontario Health Survey Mental Health Supplement showed that 38.1% of SAD cases did not complete high school, compared to 30.1% of those without SAD, and that a lifetime diagnosis of SAD was associated with a significantly greater likelihood of having failed a grade and leaving school before graduating from high school (Stein & Kean, 2000). Similarly, in a prospective study using data from the National Comorbidity Survey 10-year follow-up, baseline "internalizing fear disorders" – where SAD was the most common condition – were significantly associated with lower odds of high school graduation, although only for those that reported being non-students at the time of the first interview (i.e., 10 years before the second assessment) (Mojtabai et al., 2015). In a further study including 2,128 12-to-14 years-old Swedish students who completed a self-reported screening questionnaire for social anxiety, a total of 93 probable SAD cases were identified, of which 91.4% reported school impairment (Gren-Landell et al., 2009).

- PTSD and educational attainment

  PTSD and related symptoms following a traumatic experience are associated with low educational performance. A recent study showed negative genetic correlations between PTSD and educational attainment (Polimanti et al., 2019). A study among veterans with PTSD reported mild to moderate educational impairment related to the disorder (Morissette et al., 2019). Likewise, studies in university student samples exposed to trauma found lower academic performance and higher rates of university dropout for those individuals who developed PTSD, compared to students also exposed to traumatic events but who did not develop the disorder (Boyraz, Granda, Baker, Tidwell, & Waits, 2016; Pereira et al., 2018). In an investigation including 3,387,565 fifth-grade students from the Early Childhood Longitudinal Study, PTSD symptoms predicted lower performance scores in reading, math, and science (Goodman, Miller, & West-Olatunji, 2012). Additionally, in a nationally representative sample of young adults, 38.11% of which provided retrospective reports of childhood trauma, the odds of high school dropout among the trauma-exposed group were over twice as high, compared to those not exposed to trauma (Porche, Fortuna, Lin, & Alegria, 2011). Moreover, 750 women university students, victims of any kind of sexual assault, had lower grades than those women without history of sexual abuse (Jordan, Combs, & Smith, 2014). Other studies have assessed education-related variables in PTSD, together with some of its most frequent comorbid conditions, which have also been negatively associated with educational functioning in its own right. Furthermore, a web survey among 1,002 university students with PTSD and alcohol abuse showed lower overall academic performance and higher university dropout, compared to those without PTSD or alcohol consumption (Bachrach & Read, 2012).

  In summary, the majority of individuals living with SAD or PTSD have substantial impairments in areas relating to school and education. However, previous studies focusing on the association between SAD or PTSD and educational attainment, while valuable, generally include small samples, tend to use cross-sectional designs, explore the anxiety or stress disorders as a cluster, use retrospective self-reported measures, do not include control groups not exposed to the disorders, have a lack of control of confounders (e.g., familial factors or comorbidities) or are exclusively focused on a single milestone or age group.

  In an attempt to shed further light on the association between SAD and PTSD and educational performance, and overcome the above-listed limitations, we designed two large population-based longitudinal cohort studies including objective educational outcome data prospectively collected. Data for these studies was derived from the nationwide administrative and health records in Sweden, which are defined in the following section.

1.3 THE SWEDISH POPULATION-BASED REGISTERS

1.3.1 The Swedish national registers and the personal identification number

Several countries maintain nationwide longitudinal hospital discharge registers with mandatory individual-level reporting of diagnoses and dates for assessment and treatment. In addition to facilitating health surveillance, such registers supply ample opportunities for epidemiological research. Sweden has a tradition of nationwide registers, which contain not only health records but administrative and social information from the entire population. These registers can be linked through the personal identification number (de-identified for anonymity for research purposes) assigned to all Swedish residents at birth or immigration (Ludvigsson, Otterblad-Olausson, Pettersson, & Ekbom, 2009).

1.3.2 Specific administrative and health-related registers

Each of the relevant registers used in the studies in this thesis are briefly described below.

1.3.2.1 The Total Population Register

The Total Population Register (Ludvigsson et al., 2016) collects since 1968 sociodemographic data (e.g., sex, birth date, kinship, migration) for all inhabitants in Sweden. From the Total Population Register data, the Migration Register and the Multi-Generation Register are build. The *Migration Register* records information about individuals migrating in and out of the country, starting in 1961 for emigration and since 1969 for immigration. The *Multi-Generation Register* links individuals born in Sweden from 1932 onwards or ever registered as living in Sweden after 1960 with their biological or adoptive parents. This allows to obtain a kinship relationship for each subject, with different genetic relatedness, such as siblings. The register contains information on 100% of mothers and 98% of fathers of individuals born after 1961 (Ekbom, 2011).

1.3.2.2 The National Patient Register (NPR)

In 1964, the Swedish National Board of Health and Welfare started the *National Patient Register* (NPR). This register contains clinical diagnoses assigned by medical specialists, together with administrative data such as hospital or clinic of treatment, dates of admission and discharge, surgical procedures, and patient characteristics including age, sex, and place of residence (Ludvigsson et al., 2011). Since 1969, the NPR compiles inpatient hospital admissions and, from 1973, psychiatric care is also recorded. Since 2001, the register also includes all outpatient visits from private and public medical doctors (including day surgery and psychiatric care, but excluding primary care). Diagnoses in the NPR are coded according to the ICD system, which was adapted from the World Health Organization ICD classification system manual in

its eight (ICD-8), ninth (ICD-9), and tenth revisions (ICD-10) (Ludvigsson et al., 2011).

1.3.2.3 The National School Register

The *National School Register* contains information on educational attainment since December 31, 1988. It includes individual-level data on standardized tests taken in all subjects grades for all students from all municipal and independent schools in Sweden (The Swedish National Agency for Education, 2018).

1.3.2.4 The Longitudinal Integration Database for Health Insurance and Labour Studies

Since December 31, 1990, the Longitudinal Integration Database for Health Insurance and Labour Studies database (known as LISA for its Swedish acronym: *Longitudinell integrationsdatabas för sjukförsäkrings- och arbetsmarknadsstudier*) provides annual updated data on education, labour market, and social sectors for all individuals older than 16 years (≥ 15 years since 2010) and registered as living in Sweden (Ludvigsson, Svedberg, Olén, Bruze, & Neovius, 2019).

1.3.2.5 Other registers

The *Cause of Death Register* includes dates and causes of all deaths of Swedish residents since 1961 (Statistics Sweden, 2013). The *Conscription Register* holds information about the examination of physical and mental health, as well as cognitive function, of those individuals attending the military service between 1969 and 2010.

1.3.3 Validation of diagnostic codes in the Swedish National Patient Register

The vast Swedish nationwide registers provide unique opportunities to study risk factors as well as the long-term consequences of psychiatric disorders, among other conditions. Nevertheless, the usefulness of these studies relies on the reliability and validity of the codes used to register the information of each individual (Rosén, 2002).

Several studies have been conducted to validate diagnostic codes in the NPR via contrasting the information contained in the databases with the clinical information included in the actual medical files via chart reviews. A review of previous validation studies, mainly in somatic disorders, has shown high accuracy of the codes, with positive predictive values (PPV) ranging from 85 to 95% (Ludvigsson et al., 2011). In psychiatry, the validity of some diagnostic codes, such as obsessive-compulsive disorder (Rück et al., 2015), chronic tic disorders (Rück et al., 2015), schizophrenia (Dalman, Broms, Cullberg, & Allebeck, 2002), bipolar disorder (Sellgren, Landen, Lichtenstein, Hultman, & Langstrom, 2011) or autism spectrum disorders (Idring et al., 2012), has been also established, also showing high PPV.

To our interest, the Swedish ICD-10 code for PTSD (F43.1) in the NPR has been recently validated through medical chart review (Hollander et al., 2019). For the

validation, two raters assessed if the medical files of 158 individuals who had been diagnosed with PTSD (a F43.1 ICD-10 code was registered in the NPR), fulfilled criteria for PTSD according to DSM criteria, which was considered the gold standard definition. Results of the chart review showed that 84% of the 158 assessed cases met DSM-IV criteria for PTSD (PPV=0.84 [95% CI 0.79-0.9]) and 75% of the cases qualifyed for a PTSD diagnosis according to DSM-5 (PPV=0.75 [95% CI 0.69-0.82]). This study confirms the accuracy of the diagnostic codes registered in the NPR for PTSD, used in Study III of this thesis.

However, not all diagnostic codes for major psychiatric disorders in the NPR have been validated. A notable case was that of SAD. Hence, it was crucial to also establish the good validity of this code before being used for research purposes. This was the rational to conduct Study I of this thesis.

2 AIMS AND RESEARCH QUESTIONS

The overarching aim of this Ph.D. project was to investigate the association between SAD and PTSD and educational attainment.

The specific aims of the individual studies included in this thesis were:

Study I: To examine the validity of the ICD-10 code for SAD in the Swedish National Patient Register. This study was performed to ensure the validity and reliability of the registered codes for SAD which, unlike the PTSD codes, had not been previously established, prior to the conduction of the population-based study (Study II).

Study II: To explore the association between SAD and the educational achievement of individuals across the lifespan by means of a register-based, birth cohort study using the Swedish population.

Study III: To explore the association between PTSD and the educational achievement of individuals across the lifespan by means of a register-based, birth cohort study using the Swedish population.

3 RESEARCH STUDIES

3.1 STUDY I. VALIDATION OF THE ICD-10 CODE FOR SOCIAL ANXIETY DISORDER IN THE SWEDISH NATIONAL PATIENT REGISTER

3.1.1 Reference

Vilaplana-Pérez, A., Isung, J., Krig, S., Vigerland, S., Jolstedt, M., Bjureberg, J., Högström, J., Isomura, K., Rautio, D., Serlachius, E., Rück, C., Mataix-Cols, D., & Fernández de la Cruz, L. (2020). Validity and reliability of social anxiety disorder diagnoses in the Swedish National Patient Register. *BMC Psychiatry*, *20*(1), 242. https://doi.org/10.1186/s12888-020-02644-7

3.1.2 Background

Population-based administrative and health registers are often used for research purposes. The validity of many diagnostic codes registered in the Swedish NPR of somatic (Jakobsson et al., 2017; Sofia et al., 2014) and psychiatric diseases (Dalman et al., 2002; Idring et al., 2012; Rück et al., 2015) has been established, but the validity of many other psychiatric conditions, including SAD, is required. In Sweden, a total of 31,975 SAD cases were registered in the NPR between 1997 to 2013, with more than 3,000 new cases per year from 2008.

3.1.3 Aim

This study aimed to assess, through chart review, the validity of the recorded ICD-10 codes for SAD (F40.1), also known as social phobia, in the Swedish NPR. Additionally, to obtain information about the case representativeness of SAD diagnoses in the NPR, the symptom severity and global functioning of the patients included in the chart review were rated.

3.1.4 Summary of the methods

After approval of the study by the ethical board in Stockholm (2012/570-31/1), a sample of 300 personal identification numbers with an ICD-10 diagnosis of SAD recorded from 1998 to 2016 in the NPR was randomly selected by the Swedish National Board of Health and Welfare. The medical files of these individuals were located at clinics from all around Sweden and requested via written letters.

A total of 117 medical files were received and two independent raters reviewed each chart to assess the presence or absence of SAD, according to the definition of the ICD-10 and also according to the diagnostic criteria of the DSM-IV-TR. When disagreements between the two raters were found, a third rater reviewed the file to establish a best estimate diagnosis. After exclusion of 22 files due to lack of sufficient information to make an assessment or the SAD code missing in the actual file, the total amount of available cases for judging the validity of the code was 95. PPV (correctly diagnosed cases divided by the sum of true positive and false positives) and Cohen's κ to measure inter-rater reliability between rates were calculated. When raters considered

that a case did not meet SAD criteria (i.e., false positive), they were asked to provide the most plausible alternative diagnosis.

Additionally, in order to assess SAD symptom severity and global functioning in our sample of cases, raters completed the Clinical Global Impression – Severity (CGI-S) and the GAF rating scales for each file. Inter-rater agreement for the CGI-S and the GAF was assessed using intraclass correlation coefficients (ICC).

3.1.5 Summary of the results

Out of the final number of 95 valid cases, 77 files (81.05%) were considered to be 'true positive' cases (PPV=0.81 [95% CI 0.72-0.88]). The remaining 18 cases were not considered to fulfil neither ICD-10 nor DSM-IV-TR criteria for SAD and were, therefore, considered false positive cases. The most frequent alternative diagnoses were other anxiety disorders, depression, and autism spectrum disorders. The inter-rater agreement regarding the presence or absence of SAD was substantial (κ=0.72). CGI-S and GAF scores indicated that patients were in the moderate range of severity and functional impairment. Inter-rater agreement for the CGI-S was moderate (ICC=0.72 [95% CI, 0.54-0.82]) and good (ICC=0.82 [95% CI, 0.71-0.89]) for the GAF.

3.1.6 Main conclusions

The ICD-10 codes for SAD in the Swedish NPR are generally valid and reliable. Most patients were moderately severe and impaired, suggesting that results from register-based studies of SAD may be generalizable, specially to other treatment-seeking populations.

3.2 STUDY II AND STUDY III. ASSOCIATION BETWEEN SOCIAL ANXIETY DISORDER AND POST-TRAUMATIC STRESS DISORDER AND EDUCATIONAL ATTAINMENT

3.2.1 References

Study II: Vilaplana-Pérez, A., Pérez-Vigil, A., Sidorchuk, A., Brander, G., Isomura, K., Hesselmark, E., Kuja-Halkola, R., Larsson, H., Mataix-Cols, D., & Fernández de la Cruz, L. (2020). Much more than just shyness: the impact of social anxiety disorder on educational performance across the lifespan. *Psychological Medicine*, advanced online publication 7 January 2020. https://doi.org/10.1017/S0033291719003908

Study III: Vilaplana-Pérez, A., Sidorchuk, A., Pérez-Vigil, A., Brander, G., Isomura, K., Hesselmark, E., Sevilla-Cermeño, L., Valdimarsdottir, U. A., Song, H., Jangmo, A., Kuja-Halkola, R., D'Onofrio, B., Larsson, H., Garcia-Soriano, G., Mataix-Cols, D., & Fernández de la Cruz, L. (2020). Assessment of posttraumatic stress disorder and educational achievement in Sweden. *JAMA Network Open*, 3(12):e2028477. https://doi.org/10.1001/jamanetworkopen.2020.28477

3.2.2 Background

Both SAD and PTSD have been linked to academic underachievement, but previous studies had methodological limitations.

3.2.3 Aim

These population-based birth cohort studies aimed to further study the association between SAD (Study II) and PTSD (Study III) and objective indicators of educational attainment across the lifespan. The hypothesis was that individuals with a diagnosis of SAD (Study II) or PTSD (Study III) would have higher rates of academic underachievement across all educational levels, compared with the general population and their unaffected siblings.

3.2.4 Summary of the methods

These were register-based, observational studies with prospectively collected data resulting from linking several Swedish national registers including administrative and health information from the whole population. Both studies were approved by the Stockholm Regional Ethical Review Board (reference number 2013/862-31/5) and all procedures comply with the Helsinki Declaration of 1975, as revised in 2008. The requirement for informed consent was waived since the individuals included in the studies were de-identified. The cohort design is generally the best suited for this kind of data, including as many individuals as possible and taking advantage of the long-term follow-up for different outcome variables.

Both studies II and III used a birth cohort and applied the same quasi-experimental approach by combining study designs in order to exclude alternative explanations. Studies included:

- Comparison of the exposed individuals (i.e., those with diagnoses of SAD or PTSD) with unexposed individuals from the general population, with different adjustments.
- Comparison of the exposed individuals with their unexposed full siblings, to control for non-measured shared familial confounders.
- Analyses excluding individuals with different groups of comorbid psychiatric disorders (one at a time), to rule out that associations were explained by the presence of a comorbid disorder.
- Supplementary analyses relevant for the characteristics of each disorder and the study design.

3.2.4.1 Distribution of study populations

By means of a birth cohort design, the studies examined the association between SAD or PTSD and educational performance. To build the initial birth cohorts, all singleton

births in Sweden between January 1, 1973 and December 31, 1997 with available data up to December 31, 2013 were selected. A series of subcohorts were built with those individuals who had the sufficient time to achieve a corresponding educational milestone and did not emigrate from the country or did not die before the expected age of such achievement. All subcohorts were then followed up until December 31, 2013

The subcohorts used are described below (see **Figure 1**):

- *Compulsory education, eligibility to access upper secondary education:* Subcohort of individuals graduating compulsory school between 1998 and 2013 and not having died or emigrated from Sweden before the age of 15 years.

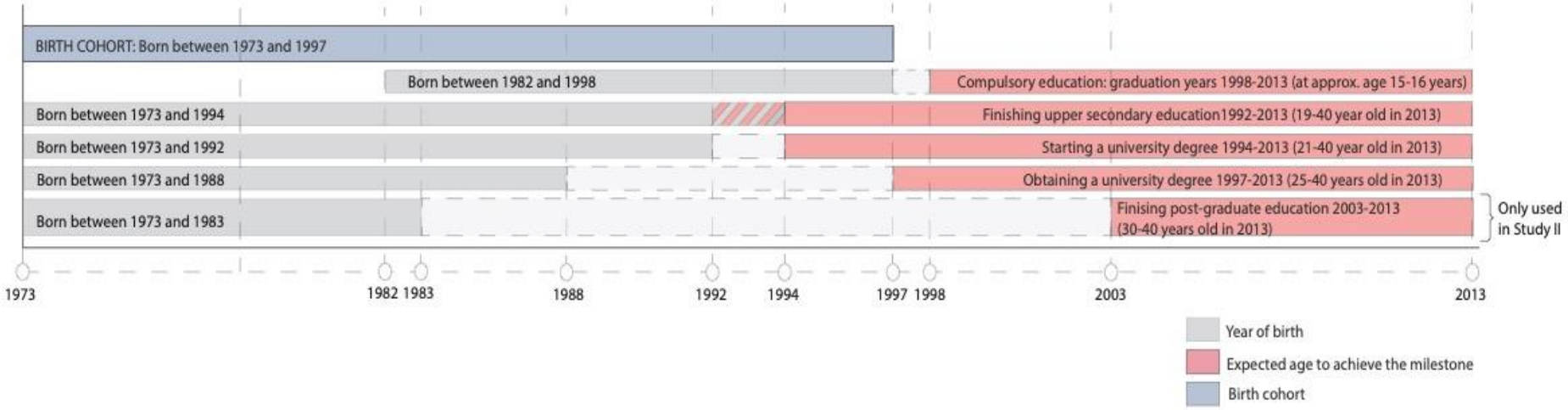
- *Finishing upper secondary education:* Subcohort of individuals born in 1973-1994 and not having died or emigrated from Sweden before the age of 19. The age range of the individuals at the end of follow-up (2013) was between 19 and 40 years old.

- *Starting a university degree:* Subcohort of individuals born in 1973-1992 and not having died or emigrated from Sweden before the age of 21. The age range of the individuals at the end of follow-up (2013) was between 21 and 40 years old.

- *Finishing a university degree:* Subcohort of individuals born in 1973-1988 and not having died or emigrated from Sweden before the age of 25. The age range of the individuals at the end of follow-up (2013) was between 25 and 40 years old.

- *Finishing post-graduate education* (only used in Study II): Subcohort of individuals born in 1973-1983 and not having died or emigrated from Sweden before the age of 30. The age range of the individuals at the end of follow-up (2013) was between 30 and 40 years old.

Figure 1. Selection of subcohorts from the main birth cohort, according to each educational milestone, included in Studies II and III.



3.2.4.2 Exposure

Exposure was defined as having a diagnosis of SAD or PTSD registered in the Swedish NPR. Details for each of the register-based studies regarding the exposure variable are provided below.

Study II: Treatment-seeking individuals with a lifetime diagnosis of SAD according to the ICD-10 definition (code F40.1), as recorded in the NPR. A minimal age threshold of 6 years for being diagnosed with SAD was set in order to avoid misclassifications. Individuals with no diagnoses of SAD in the NPR under the study period were considered unexposed.

Study III: Individuals with a recorded ICD-10 PTSD diagnosis (code F43.1) in the NPR. To capture the association between PTSD and educational achievement within each subcohort, we collected the diagnosis of PTSD recorded at age ≥6 years (to avoid misclassifications), but prior to the expected age of completion of each educational milestone. Thus, for each subcohort, PTSD diagnoses were used to denote the exposure status if recorded between 6 and 16 years for compulsory education, 6-19 years for finishing upper secondary education, 6-21 years for starting university degree education, and 6-25 years for obtaining university degree. For each educational milestone, individuals with no PTSD diagnoses recorded in the corresponding age interval were considered unexposed.

3.2.4.3 Outcomes

The educational outcomes assessed in association with the exposure were the following academic milestones:

- Compulsory Education

The Swedish primary and lower secondary education are compulsory and take 9 years to complete (generally finished at ages 15-16). A subcohort of individuals graduating between 1998 and 2013 was used for this analysis.

The Swedish compulsory school system includes 16 compulsory subjects, for which the students are awarded the final grades upon graduation. Swedish language, English language, and mathematics are considered to be core subjects, which means that they are given extra weight in the eligibility to access upper secondary education. Final grades determine students' eligibility to access either vocational programs, with a primary aim of preparing for working life, or academic programs, which prepare for further academic studies at upper secondary school. Study II focused on both eligibility for vocational and academic programs, while Study III only focused in the vocational program outcome, since its requirements are less stringent. A student is considered eligible for a vocational program if a *pass* grade in the core subjects is achived, and,

since 2011, it is also required to pass five additional subjects. Academic programs require a *pass* grade in Swedish, English, and mathematics, and in nine additional subjects. From the National School Register, we retrieved information on the eligibility to access upper secondary school for both Studies II and III**,** and the information on individual grades for each participant in Study II.

- Post-compulsory education

  The database LISA was used to retrieve data on the following binary post-compulsory educational outcomes (recoded as achieved *vs.* not achieved) for the cohorts in both studies: finishing upper secondary education, starting a university degree, obtaining a university degree, and, only for Study II, finishing postgraduate education (i.e., a master's or a doctoral degree).

3.2.4.4 Covariates

In all observational studies, there are factors that are suspected to be associated with both, the exposure and the outcome, thereby confounding potential associations between them. For example, parental age at childbirth might increase the risk for SAD and, independently, the risk for educational failure. In order to examine as much of the true association as possible, potential confounders such as demographic variables were adjusted for, including birth year, sex, and age of the mother and age of the father at the time of birth of the individual. This information was retrieved from the Total Population Register.

From the NPR, we also extracted all lifetime psychiatric comorbidities for the members of our cohorts: (1) neuropsychiatric disorders (including pervasive developmental disorders, attention-deficit/hyperactivity disorder, Tourette syndrome and chronic tic disorder, and learning disabilities); (2) conduct disorder (only in Study III); (3) other phobic, anxiety, obsessive-compulsive, and reaction to severe stress and adjustment disorders (last cluster of F43 family, only employed in study II); (4) eating disorders (only in Study III); (5) psychotic disorders (including schizophrenia, schizotypal, and delusional disorders); (6) affective disorders (including bipolar disorder, depressive disorders, and persistent mood disorders); and (7) substance use disorders.

Since previous studies have shown that lower level of intelligence (albeit within the normal range) may be a risk factor for developing PTSD (DiGangi et al., 2013; Kremen et al., 2007), we wanted to account for the impact that this variable might have on the association between PTSD and educational performance in Study III. In order to do this, from the Conscription register, we selected within each abovementioned subcohort a subsample of men born in Sweden between 1973-1997 who attended the mandatory military service at age 18 years and underwent assessment of their general cognitive ability in the context of the conscription testing.

3.2.4.5 Data analysis

For both studies, data management was performed using SAS, version 9.4 (SAS Institute, Cary, NC, USA) and analyses were completed on STATA version 15.1 (Stator LLC, College Station, TX, USA).

Logistic regression models were fitted to obtain odds ratios (ORs) and corresponding 95% confidence intervals (CIs) in order to explore the association between SAD or PTSD and each binary educational outcome. Each outcome was assessed within a corresponding subcohort (i.e., among the individuals who were alive and living in Sweden at the age 'old enough' to start or complete a corresponding educational level). For study III (PTSD), a logistic regression model was fitted considering as exposed those individuals with a recorded diagnosis of PTSD before they started or completed the corresponding educational level under study. Crude models were followed by models adjusted for sex, birth year, and maternal and paternal age at childbirth. As data within family or individual clusters tend to be positively correlated, this non-independence of clustered data needs to be addressed in order to not underestimate standard errors (the bases for confidence intervals and statistical significance testing). Hence, analyses for each subcohort were clustered by mother identification number (in order to also keep those individuals without information from fathers, for ecological reasons) with a robust sandwich estimator of standard errors, which provided more stringent definitions of statistical significance (Williams, 2000).

Moreover, there could be other unmeasured factors that better explain the associations. A useful method to control for some unmeasured confounders is to compare full siblings within the same family (i.e., those sharing the same mother and the same father) that are discordant for the exposure. By doing so, variables such as shared environmental factors (e.g., early socioeconomic status, parental education, parental history of somatic and psychiatric disorders) and about 50% of the genetic liability are held constant in the analyses. If, for example, socioeconomic status was associated with both the exposure (e.g., having SAD or PTSD) and the outcome (e.g., educational outcomes), comparing siblings from the same family would effectively control for this confounder. To explore the association accounting for those unmeasured factors, a fixed-effects model was implemented within the subsamples of full siblings discordant for SAD (study II) or PTSD (study III), where each family was considered a stratum. For the analyses of the association between the educational outcomes and a lifetime exposure to SAD, the sibling was defined as unexposed if no lifetime SAD diagnosis was recorded. For the analysis where an exposure was defined as a diagnosis of PTSD recorded prior to the educational milestone, the sibling was defined as unexposed if he/she had no records of PTSD prior to the age that refers to achieving the educational milestone in question. As above, models were adjusted for sex, birth year, and parental ages at childbirth, and a robust sandwich estimator of standard errors was implemented to account for non-independence of observations within families (Williams, 2000).

Further analyses were performed in both Studies II and III to assess the extent to which psychiatric comorbidities could explain the associations between SAD or PTSD and each educational milestone. To this end, the main analyses were repeated after excluding individuals with comorbid psychiatric disorders (one group of comorbid disorders at a time). In Study III (PTSD), psychiatric disorders (all at once) were also used as an adjusting variable in the main model.

Also in Study III, we performed a series of supplementary analyses. First, we adjusted the models for the previous milestone, expressed as a binary outcome (pass or not pass), in order to control for the carry-over effect of not passing a previous milestone on the achievement of the upper milestones. Second, the main analyses were repeated for the subset of men (within each subcohort) who underwent conscription examination. For this analysis, we additionally adjusted for the measure of general cognitive ability.

3.2.5 Summary of the results

3.2.5.1 Study II

The birth cohort included 2,238,837 individuals born in Sweden between 1973 and 1997. Within the cohort, 15,755 individuals had a recorded ICD-10 diagnosis of SAD in the Swedish NPR. The proportion of women in the SAD cohort (8,706; 55.3%) was significantly larger than that in the non-exposed cohort (1,081,036; 48.7%). Out of the initial cohort, 1,425,340 individuals were assessed for finishing compulsory education (10,093 with SAD), 1,998,971 individuals for finishing upper secondary education (14,997 with SAD), 1,794,981 for starting a university degree (13,901 with SAD), 1,356,841 for obtaining a university degree (10,731 with SAD), and 899,325 for finishing post-graduate education (6,680 with SAD).

Compared to unexposed individuals, individuals diagnosed with SAD were less likely to pass all subjects in the last year of compulsory education (adjusted OR [aOR] ranging from 0.19 to 0.44) and less likely to be eligible for a vocational (aOR=0.31 [95% CI, 0.30–0.33]) or an academic program (aOR=0.52 [95% CI, 0.50–0.55]) in upper secondary education, finish upper secondary education (aOR=0.19 [95% CI, 0.19–0.20]), start a university degree (aOR=0.47 [95% CI, 0.45–0.49]), obtain a university degree (aOR=0.35 [95% CI, 0.33–0.37]), and finish postgraduate education (aOR=0.58 [95% CI, 0.43–0.80]). Regarding sex differences, girls showed statistically significant more impairment than boys across all educational levels, except for finishing post-graduate education. The educational level presenting the largest sex difference was starting a university degree (aOR for women = 0.43 [95% CI, 0.40–0.45] *vs.* aOR for men = 0.54 [95% CI, 0.51–0.58]).

In adjusted sibling comparison models, results were attenuated (aOR ranging from 0.31 to 0.63), indicating that part of the observed associations were explained by factors shared by siblings, including genetic and shared familial factors, but remained statistically significant. When psychiatric comorbidities were taken into account, the results were largely unchanged.

3.2.5.2 Study III

Out of the initial cohort of 2,244,193 individuals (48.7% women), 1,425,326 individuals were assessed for finishing compulsory education (919 with prior PTSD), 2,001,944 individuals for finishing upper secondary education (2,013 with prior PTSD), 1,796,407 for starting a university degree (2,243 with prior PTSD), and 1,356,741 for finishing a university degree (2,254 with prior PTSD). A diagnosis of PTSD was associated with lower odds of achieving each of the assessed educational milestones during the study period, including 82% lower odds of finishing compulsory education (aOR=0.18 [95% CI, 0.15–0.20]), 87% lower odds of finishing upper secondary education (aOR=0.13 [95% CI, 0.12–0.14]), 68% lower odds of starting a university degree (aOR=0.32 [95% CI, 0.28–0.35]), and 73% lower odds of obtaining a university degree (aOR=0.27 [95% CI, 0.23–0.31]). Sex differences were not significant.

Estimates in the sibling comparison remained significant, but the magnitude of the ORs approximately halved (aOR ranging from 0.22 to 0.53). Excluding psychiatric comorbidities, adjusting for the successful completion of the previous milestone, and general cognitive ability had little effect on the magnitude of the associations.

3.2.6 Main conclusions

Individuals with SAD, especially women, were less likely to pass all subjects in compulsory education and were also less likely to achieve all the educational milestones under study, from compulsory education to post-graduate education, compared to individuals from the general population.

Individuals with PTSD diagnosed before the expected age of achievement of each milestone were consistently less likely to achieve all educational milestones under study, spanning from compulsory education to finishing university, compared to individuals from the general population.

The results in both studies remained, although attenuated, after strict control for shared familial factors. This attenuation suggests that shared familial factors are potentially important in explaining the association between SAD or PTSD and educational attainment. When psychiatric comorbidities (and general cognitive ability in Study III) were taken into account, overall results remained largely unchanged.

Collectively, these results strongly suggest that SAD and PTSD are associated with profound impairments on educational performance over and above familial factors, psychiatric comorbidities, and general cognitive ability for PTSD. Although these results are not specific to SAD or PTSD – academic difficulties have also been described in other psychiatric disorders using similar methods (Dalsgaard et al., 2020; Pérez-Vigil, Fernández de la Cruz, Brander, Isomura, Jangmo, Feldman, et al., 2018; Pérez-Vigil, Fernández de la Cruz, Brander, Isomura, Jangmo, Kuja-Halkola, et al., 2018) – the impact of PTSD, and to a smaller extent of SAD, on educational performance seems to be more pronounced than in other conditions. Early detection of these disorders and early intervention strategies not only in a mental health contexts but also in educational settings are warranted to minimise the long-term socioeconomic consequences of these disorders.

4 DISCUSSION

SAD and PTSD are highly disabling disorders. The disabilities extend to several areas of the life of the individual, such as their personal, familiar, social, and professional life, including the academic domain. As referred above, previous efforts to evaluate the impact of SAD and PTSD on educational performance have been hindered by several limitations. Hence, the overall aim of this thesis sought to explore the association between SAD and PTSD and educational performance by using sound methodology and the large population-based Swedish registers. The main finding of this thesis was that individuals with SAD or PTSD are consistently less likely to achieve all educational milestones across the lifespan, over and above a number of confounders such as familial factors and psychiatric comorbidities. These findings will inform the development of interventions to palliate this impact.

4.1 VALIDATION STUDY

As a preliminary step for the register-based studies, we conducted the validation of the SAD code in the NPR, obtaining a good PPV (81% of the cases assessed were "true positives" and met criteria for SAD) and a substantial inter-rater agreement. Furthermore, through severity and global functioning measures, we concluded that most part of the individuals in the sample belonged to the moderately ill category, according to the CGI-S, and that their overall impairment was moderate, according to the GAF. These mesures offered information that was not previously available on the severity and functional impairment status of the individuals diagnosed with SAD in the registers. This information is crucial in order to be able to generalize the results of studies employing the SAD code in the NPR to other treatment-seeking populations.

This, together with the already-reported good validity of the PTSD code (84% of the assessed clinical files met criteria for PTSD according to DSM-IV criteria) (Hollander et al., 2019), ensured that the planned educational outcomes studies could use exposure variables that were valid an reliable.

4.2 EDUCATIONAL OUTCOMES STUDIES

4.2.1 Main findings

Thus, employing valid codes, our nationwide cohort studies showed that individuals with SAD or PTSD were consistently less likely to achieve all educational milestones under study, compared both to individuals from the general population and also to their unaffected siblings.

Individuals with a SAD diagnosis, compared to individuals from the general population, were significantly less likely to pass all subjects in the last year of compulsory education, which in Sweden is a previous step for being eligible to access upper secondary school. On average, persons with SAD had between 42% to 81% lower odds of completing the educational milestones, spanning from compulsory to

post-graduate education. Likewise, individuals with prior PTSD had between 68% to 87% lower odds of finishing the different educational levels, ranging from compulsory school to finishing university.

In our studies, the strongest results (i.e., higher risk of not achieving that milestone) were for the completion of upper secondary education. The odds of achieving this milestone were 81% lower for individuals with SAD and 87% lower for individuals with prior PTSD, compared to those without either disorder. In Sweden, the average percentage of adults who completed upper secondary education is 83% (OECD, 2019a), in line with our results, where 81% of individuals without SAD or PTSD in the cohort completed this educational level. In contrast, only 46% of individuals with SAD and 33% of individuals with prior PTSD were able to complete upper secondary education. This particular level is of crucial importance since it is the first step after compulsory education. In fact, not completing upper secondary studies is associated with greater difficulty to access university, adds a disadvantage when individuals apply and try to maintain a job later on, and, specially for men, is associated with more sick leave and disability (Hoff et al., 2018).

In the same line, failure in upper educational levels was also associated with the diagnosis of one of our disorders of interest. Individuals with SAD had 53% lower odds of starting a university degree, 65% lower odds of obtaining the degree, and 42% lower odds of achieving post-graduate education. In case of a prior PTSD, the odds were 68% lower to start and 73% lower to finish a university degree, compared to individuals without the disorder within the same age range. These results match previous, much smaller reports showing that SAD and PTSD play a role on whether students remain enrolled or achieve a university degree (Auerbach et al., 2016; Boyraz et al., 2016; Boyraz, Horne, Owens, & Armstrong, 2013; Davidson et al., 1994; Gren-Landell et al., 2009; Kessler, 2003; Lijster et al., 2018; Ohayon & Schatzberg, 2010; Pereira et al., 2018; Ranta, La Greca, Kaltiala-Heino, & Marttunen, 2016; Stein & Kean, 2000), although our studies focused on a broader range of milestones, spanning over several years of the educational pathway of the population.

4.2.2 Sex differences

Women born in the 1950s and onwards have rapidly increased their participation in educational settings (Pekkarinen, 2012) and, nowadays, women are the majority among secondary and tertiary school graduates, widening the educational gender gap (Van Hek, Kraaykamp, & Wolbers, 2016). This matches the distribution in the Swedish population, as showed in our studies, where more women than men accessed all education levels, regardless of their exposure status for either disorder (except for post-graduate education, only assessed in Study II). Nonetheless, we also reported that women with SAD had statistically significant lower odds of achieving most educational milestones, particularly starting university, compared to men with SAD. These results

are in line with previous literature reporting that girls with SAD had greater scholastic underachievement (Baptista et al., 2012). Similarly, a recent Danish population-based study found that, for individuals with anxiety (including SAD), insecure attachment, attention-deficit/hyperactivity, and other developmental disorders, girls attained relatively lower standardized mean grades, compared with their boys counterparts (Dalsgaard et al., 2020). A possible explanation for the greater impairment in women could be the fact that girls generally tend to achieve higher grades (Voyer & Voyer, 2014) which would lead to a more noticeable effect, compared to a general population group, when they have some kind of added difficulty (e.g., a diagnosis of a psychiatric disorder). Moreover, parents and teachers tend to perceive girls with SAD as less impaired than boys with SAD (Sellers, Maughan, Pickles, Thapar, & Collishaw, 2015), which could lead to providing less support to girls in need for it.

In contrast, however, sex differences in the PTSD study were not statistically significant across all milestones, meaning that both genders had the same odds to complete the milestones and that all individuals with PTSD, regardless of sex, were more impaired than their counterparts without the disorder.

4.2.3 Role of the psychiatric comorbidities

Psychiatric disorders are highly comorbid (Andrews, Slade, & Issakidis, 2002). In fact, in both our cohorts, more than 83% of individuals with SAD or PTSD were diagnosed with other psychiatric disorders, compared to less that 14% of individuals without SAD or PTSD. Sistematically removing various groups of psychiatric disorders from our analyses attenuated but did not substantially affect the results for either the SAD or PTSD main models. In the case of PTSD, this is in contrast with a previous, much smaller study reporting worse educational outcomes in individuals with self-reported PTSD and alcohol use, compared to PTSD alone (Bachrach & Read, 2012). Also for PTSD, a further analysis which adjusted for all psychiatric comorbidities at the same time did not explain the observed associations either. Thus, based on this, it would seem that both our disorders of interest are associated with educational underachievement, independently from the presence of other psychiatric comorbidities that could account for this association.

4.2.4 Covariate adjustment

Intelligence has a well-established relation with educational attainment (Lynn & Mikk, 2009). For SAD, to the best of our knowledge, no correlation between the disorder and intelligence has been established. By contrast, in the case of PTSD, lower premorbid intelligence has been previously considered a risk factor for the disorder (Kremen et al., 2007; Nissen et al., 2017). In this line, our results for conscripted men with information on the cognitive ability variable showed significantly lower scores on this variable in the group of men with PTSD, compared to those without PTSD. Nonetheless, after adjusting our models for general cognitive ability, men with PTSD still had a worse

academic performance across the various milestones, compared to men without PTSD (except for starting university, potentially due to limited power), indicating that the effect on the educational performance is likely to be independent from the level of cognitive ability.

Adittionally, one could assume that completing an educational milestone increases the probability to achieve an upper milestone. Hence, in Study III, we adjusted the models for the conditional completion of the previous milestone. By doing this, the results were attenuated but did not significantly change, suggesting that the predictable progression in the educational pathway was not sufficient to explain the association between PTSD and lower educational achievement. A possible explanation could respond to the charateristics of the Swedish educational system, which is non-linear and allows individuals to take higher educational milestones without necessarily having to pass the lower ones by allowing for different alternatives to get the required qualifications, such as the locally funded school system for adults who have failed to complete primary or secondary school (known as *Komvux* in Sweden).

4.2.5 Sibling comparisons

The discordant sibling design provided unprecedented control of unmeasured confounders (environmental and genetic factors) shared by full siblings. The sibling comparison showed that siblings with a diagnosis of SAD or PTSD were also more educationally impaired than their unaffected siblings. Comparing these results with our main analyses, we noticed that the magnitude of the associations was attenuated, which may suggest that some shared familial factors (either genetics or shared environment) are relevant in explaining at least part of the association between SAD or PTSD and educational attainment. This was particularly relevant in the case of PTSD, where the magnitude of the odds ratios approximately halved in the sibling comparison, compared to the population comparison. Besides, educational attainment is generally heritable to a high degree (Rimfeld et al., 2018; Shakeshaft et al., 2013). In the particular case of PTSD, it is possible that shared genetic effects may partially explain both, a higher risk of the disorder and a diminished educational performance (Polimanti et al., 2019; Rimfeld et al., 2018; Shakeshaft et al., 2013). Further, our results are also in line with previous studies (Esch et al., 2014; Schlechter & Milevsky, 2010) suggesting that shared environmental risk factors, such as socioeconomic status, ethnicity, parental history of mental disorders or parental educational level (which have been previously associated with school performance in the offspring in their own right), partially controlled by this design, may be additional contributing factors to the observed association between educational performance and SAD or PTSD.

Nonetheless, the control for shared familial factors did not completely account for the results, suggesting as well that the presence of SAD itself, or PTSD itself, may constitute an important predictor of lower educational attainment, independently from

shared genetics and shared environment. It remains to be explored whether non-shared genetic or environmental factors, not accounted for in our sibling models, could explain some part of the variance in the described associations.

4.2.6 Comparison with previous large-scale epidemiological studies

A comparison with previous cohort studies examining educational outcomes in other psychiatric disorders and using similar methods shows that our results in SAD and PTSD are likely not specific to these disorders, but rather, a similar pattern of scholastic difficulties can be observed in a range of different psychiatric disorders. In this line, our results are comparable, for example, to those reported in a comprehensive recent Danish study, which showed a lower proportion (0.52; 95% CI, 0.52-0.53) of individuals with a mental disorder taking the final examination of ninth grade (a similar milestone to the eligibility at the end of compulsory school in our study), compared with individuals without a mental disorder (0.88; 95%CI, 0.88-0.88) (Dalsgaard et al., 2020). Of note, however, the Dalsgaard *et al.* (2020) study did not include PTSD, while SAD was included in a broad category encompassing anxiety disorders and OCD. Therefore, our studies add value to the literature by reporting information on two further, separate phenotipes.

Despite the above-mentioned likely lack of specificity between psychiatric disorders, and leaving aside some methodological differences between studies, it seems that individuals with a prior diagnosis of PTSD, and to a smaller extent of SAD, are at higher risk of educational underachievement than patients with other psychiatric disorders such as OCD or with Tourette syndrome or chronic tic disorder, as showed by two previous studies also conducted using the Swedish registers. In these studies, individuals with OCD were 57% less likely to complete upper secondary education (aOR, 0.43; 95% CI, 0.41-0.44), 28% less likely to start a university degree (aOR, 0.72; 95% CI, 0.69-0.75), 41% less likely to finish a university degree (aOR, 0.59; 95% CI, 0.56-0.62), and 48% less likely to complete postgraduate education (aOR, 0.52; 95% CI, 0.36-0.77), compared with those without OCD; on the other hand, individuals with tic disorders were 65% less likely to complete upper secondary education (OR, 0.35; 95% CI, 0.32-0.37), 59% less likely to start a university degree (OR, 0.41, 95% CI, 0.37-0.46), and 61% less likely to finish a university degree (OR, 0.39, 95% CI, 0.32-0.48), compared to individuals without tic disorders (Pérez-Vigil, Fernández de la Cruz, Brander, Isomura, Jangmo, Kuja-Halkola, et al., 2018). Taking finishing upper secondary education as a reference category, these studies and our own results in SAD and PTSD, all four conducted within the same population, would compare as follows: odds of reaching this milestone would be 87% lower for individuals with prior PTSD, 81% lower for individuals with SAD, 59% lower for individuals with Tourette syndrome or chronic tic disorder and 57% lower for individuals with OCD.

4.3 CLINICAL AND SOCIAL IMPLICATIONS

Our results highlight the importance of adressing the functional impairment of individuals suffering from psychiatric disorders. In particular, since the results confirmed the clinical impression that SAD and PTSD are associated with educational impairment, actions should be taken to improve the academic underachievement of these individuals. This would be an important measure because educational attainment has shown to be a social determinant of health, including mental health (Winters et al., 2005), and has an impact on neural development, biological aging, and health-related behaviors (Cohen & Syme, 2013).

Some early interventions to promote mental well-being, improve functionality, and intervene on these disorders, besides improving the academic performance, have been implemented in schools since the benefits of the school-based context are several. Schools offer a great scenery for frequent observation by teachers and staff, allowing for naturalistic exposures, real-world practice, and skills generalization (Sweeney et al., 2015). In addition, interventions in schools are well acccepted for the parents because they are generally less stigmatizing than those delivered in mental health contexts (Storch & Crisp, 2004). Further, they can constitute early interventions for some difficulties and disorders that could otherwise be left untreated (de Girolamo, Dagani, Purcell, Cocchi, & McGorry, 2011).

Over the last decades, a wide although heterogeneous group of school mental health programmes have emerged (Paulus, Ohmann, & Popow, 2016), showing evidence of reducing symptomatology, enhancing interventions delivered in mental health settings, reducing risky behaviors, promoting coping skills, and also improving educational attainment (Lereya, Patel, dos Santos, & Deighton, 2019; OECD, 2018; Weare & Nind, 2011). A meta-analysis of 213 school-based programmes aiming to promote well-being and emotional literacy among students found that their implementation was also associated with an 11% improvement in academic performance (Durlak, Weissberg, Dymnicki, Taylor, & Schellinger, 2011). These school-based mental health programmes have shown to promote academic achievement throughout different educational milestones (Reynolds, Ou, & Temple, 2018), since individuals who struggle during early educational stages but receive adequate support and guidance have higher probabilities of achieving further milestones, despite potential difficulties in their family or social background (OECD, 2012).

Programmes can be universal (i.e., targeting the entire population) or targeted, being either selective (i.e., targeting individuals whose risk of developing a psychiatric disorder is significantly higher than average, based on a certain characteristic, for example, on family history of the disorder) or indicated (i.e., targeting high-risk children with certain risk factors or who already have incipient difficulties potentially foreshadowing a psychiatric disorder but still sub-clinical symptoms) (World Health

Organization, 2004). The majority of these programmes are designed for universal prevention and promotion of the students' well-being in general (McDaid, Hewlett, & Park, 2017; Patalay et al., 2017). One exemple of a primarily preventive and universally implemented programme for mental health problems is *Zippy's Friends*, which aims at developing social and emotional coping skills and emotional learning for 5 to 7 year olds (Clarke, Bunting, & Barry, 2014). It has been implemented in 27 countries, and has helped to reduce bullying and, to a lesser extent, to improve academic scores (Holen, Waaktaar, Lervåg, & Ystgaard, 2013). As for the targeted or indicated programmes, a recent meta-analysis has reported that, particularly for anxiety, they may be more effective over time than the universal programmes (Hugh-Jones, Beckett, Tumelty, & Mallikarjun, 2020).

As for specific programmes aimed at our disorders of interest, SAD and PTSD, some universal and targeted prevention and intervention programmes have been developed and implemented with good results (Rolfsnes & Idsoe, 2011; Scaini, Belotti, Ogliari, & Battaglia, 2016). In the case of SAD, it is known that many feared situations for children are encountered in school settings, including group tasks, talking to teachers or giving oral presentations. These situations can trigger their hyper-arousal symptoms (e.g., blushing, trembling, sweating), hindering their attention to academic knowledge, judging their competence poorly (Ohayon & Schatzberg, 2010), and commonly leading to avoidance of these situations (Van Ameringen et al., 2003). Targeted school-based interventions to detect and reduce these SAD symptoms have several advantages over individual treatments, as they have demonstrated larger effect sizes in a meta-analysis (Scaini et al., 2016), in part because they focus on early recognition of SAD symptoms by peers and school staff (Masia Warner et al., 2016; Masia Warner, Fisher, Shrout, Rathor, & Klein, 2007; Masia Warner et al., 2005). For example, a two-step screening programme of social anxiety symptoms to detect SAD cases in a high school context, including self-report measures and a brief phone interview with parents, has proved to be effective (Sweeney et al., 2015). Additionally, intervention programmes generally used in clinical practice for SAD have been adapted to school contexts to treat and help young people with SAD progress in their educational goals. For instance, the Social Effectiveness Therapy for Children (SET-C) programme (Beidel, Turner, & Morris, 2000) was adapted into the 12-week Skills for Academic and Social Success (SASS) programme (Masia Warner, Colognori, & Lynch, 2018), which was shown to be superior than a non-specific counselling in reducing social anxiety and increasing school functioning in 138 high school students (Masia Warner et al., 2016).

Regarding PTSD, individual responses after the exposure to traumatic events, and presumably, the core symptoms of PTSD, such as re-experiencing, hyperarousal, dissociation, and sleep problems (American Psychiatric Association, 2013) can interfere with school functioning by means of impaired attentional or memory resources (Scott et al., 2015), increased learning difficulties, absenteeism, lower grades,

need for special education or disruptive behaviors accompanied with suspension (Substance Abuse and Mental Health Services Administration, 2014; Van der Kolk, Roth, Pelcovitz, Sunday, & Spinazzola, 2005). There are interventions which may help deal with traumatic situations, such as the trauma-informed approach of teaching methodology adopted in many schools, responding to the fact that approximately two out of three children are likely to have experienced at least one or more traumatic events by age 17 (Substance Abuse and Mental Health Services Administration, 2014), and a substantial percentatge of them will develop a PTSD (Porche, Costello, & Rosen-Reynoso, 2016; Rolfsnes & Idsoe, 2011; Rossen & Hull, 2013). This approach, which aims to raise awareness and prevent consequences of experiencing traumatic experiences, requires a change in the educational phylosophy of the school where all staff adopt 6 principles: safety whithin interactions; trustworthiness and transparency of decisions; peer (as trauma survivors) support; collaboration and mutuality for all staff and students; empowerment of individual strenghts; and comprehensive approach for cultural, historical and gender issues (Substance Abuse and Mental Health Services Administration, 2014). By means of this approach, the school has the chance to become a secure attachment place and help to avoid re-traumatizations (Van der Kolk et al., 2005). In addition to the general trauma-focused approach, programmes targeting students with identifiable PTSD symptomatology have been implemented, showing good results at reducing symptoms in a meta-analysis of 19 programmes (Rolfsnes & Idsoe, 2011). Among these interventions in schools and universities are, for example, the Cognitive Behavioral Intervention for Trauma in Schools (Hoover et al., 2018; Jaycox, Kataoka, Stein, Langley, & Wong, 2012), a 10-week group and individual therapy programme for parents and teachers (Vona et al., 2014); the Enhancing Resiliency Amongst Student Experiencing (ERASE)-Stress programme, which has been reported to lower PTSD symptoms and depression among students (Berger & Gelkopf, 2009); and the RAP Club, a 12-session school-based trauma-informed group intervention based on cognitive-behavioral and mindfulness strategies (Mendelson, Tandon, O'Brennan, Leaf, & Ialongo, 2015).

Since these mental health interventions in schools may contribute to improve not only the psychiatric symptoms but also the educational outcomes, they have the potential to reduce the associated societal and economic burden linked to the disorders. A better adaptative functioning may help reducing indirect costs such as those related to caregivers (i.e., for children in school age, their parents) (Kalra, Kamath, Trivedi, & Janca, 2008). Further, the level of educational achievement can predict labour-related outcomes in the individual (Shavit & Muller, 1998), and in most countries, individuals who have achieved higher educational milestones have higher salaries than individuals with less years of education (OECD, 2019a), which may reduce the opportunity costs and the DALY index (Wittchen et al., 2011). In this line, the described educational difficulties in individuals with SAD and PTSD can be assumed to negatively impact on work-related variables in these groups, which would become more vulnerable. In fact,

it is known that individuals with psychiatric disorders have higher rates of labour market marginalisation, including long-term unemployment, long-term sickness absence, and higher rates of disability pension (Gabriel & Liimatainen, 2000; Helgesson, Tinghög, Niederkrotenthaler, Saboonchi, & Mittendorfer-Rutz, 2017; Niederkrotenthaler et al., 2016; Pérez-Vigil, Mittendorfer-Rutz, Helgesson, Fernández de la Cruz, & Mataix-Cols, 2019). Hence, intervening on these psychiatric disorders and in the impact that they have on education at early stages could contribute to palliate economic disparities and ameliorate labour outcomes for these individuals (Belfield, 2007; OECD, 2012).

4.4 RESEARCH IMPLICATIONS

There is a growing interest from professionals, governments, and institutions on assessing and intervening on the functional impairment caused by psychiatric disorders and its broad consecuences (James et al., 2018). In the last decade, the adoption of a common biopsychosocial framework and the development of the ICF and the WHODAS (Federici, Bracalenti, Meloni, & Luciano, 2017; Ustün et al., 2010) has contributed to an increased volume of research aiming at quantifying educational impairment in the general population (OECD, 2019a, 2019b). Furthermore, some recent studies have focused on vulnerable populations, such as those with psychiatric disorders, associating a number of conditions with a more significant academic impairment (Dalsgaard et al., 2020; Pérez-Vigil, Fernández de la Cruz, Brander, Isomura, Jangmo, Feldman, et al., 2018; Pérez-Vigil, Fernández de la Cruz, Brander, Isomura, Jangmo, Kuja-Halkola, et al., 2018; Wickersham et al., 2020) At this point, it would be useful to determine the specific mechanisms underlying this association. For example, unmeasured confounders shared within families such as parental history of somatic or psychiatric disorders have been scarcely taken into account in prior studies. Nonetheless, both register-based studies in this thesis, as well as others also using the Swedish registers (Pérez-Vigil, Fernández de la Cruz, Brander, Isomura, Jangmo, Feldman, et al., 2018; Pérez-Vigil, Fernández de la Cruz, Brander, Isomura, Jangmo, Kuja-Halkola, et al., 2018), have determined that, despite familial factors could account for part of this association, psychiatric disorders seem to contribute to a worse educational attainment in its own right. Further efforts made to disentangle the etiological contributions to this association may be useful in designing preventive strategies and outreach programmes for improved educational performance (Mojtabai et al., 2015), smoothing the school-to-work transition (OECD, 2019a).

As previously mentioned, SAD and PTSD have also labour and economic consequences (Aderka et al., 2012; Olatunji et al., 2007; Wald & Taylor, 2009). To quantify the labour market and economic impact of these disorders is a future line of research worth pursuing, since it would be an important benchmark to develop policies by stakeholders, governments, and institutions and guarantee an improved quality of life for the affected individuals.

4.5 STRENGTHS AND LIMITATIONS

The main strength of the studies included in the thesis was the use of the large population-based Swedish registers, which include health data and objective educational outcome data prospectively collected. These data ensured minimal risk of selection, social desirability, and memory biases. Other strengths included the fact that codes for the psychiatric disorders under study were validated, with good results; the follow-up period of over 20 years allowed sufficient time for the various cohorts to reach the relevant educational milestones, including post-graduate studies; the use of quasi-experimental family designs with the discordant sibling comparation, which allowed us to control for relevant confounders shared by full siblings, including about 50% of the genetic load and shared environment; and the fact that a wide range of psychiatric comorbidities were taken into account in order to provide more accurate estimates of the association between SAD and PTSD and educational outcomes.

On the other hand, this thesis also has to be understood in the context of several limitations. A detailed acount of the limitations of the studies included in this thesis can be found in the respective publications. However, this section offers a summary of the most relevant.

In Study I, we were only able to collect, and therefore assess, about one third of the initially requested cases, which may suggest a potential selection bias of unknown nature. Additionally, the raters were not blind to the register diagnoses, which may have increased the risk of bias towards confirming the SAD diagnoses. Lastly, raters scored the CGI-S and the GAF based on the chart review, without directly interviewing the patients. The validity of these scales when used in this format is unknown and, therefore, the results should only be viewed as broad clinical impressions of the patients' severity and general function. Nonetheless, the inter-rater agreement was adequate for both instruments.

For Studies II and III, a source of measurement error might have been the misclassification of the individuals in our cohorts. Patients included in the NPR are treatment-seeking individuals diagnosed by specialists. Hence, the number of available cases of SAD or PTSD in the registers is lower than the expected prevalence of these disorders in the population. Thus, the generalizability of the findings to non-treatment seeking persons or individuals diagnosed by general practitioners or non-medical professionals (e.g., psychologists) could have been compromised. Further, outpatient care records were only available from 2001, and because SAD and PTSD do not usually require hospitalization, the vast majority of diagnosed cases in our cohort were collected from 2001 onwards. These limitations also apply to the identification of the psychiatric comorbidities. Moreover, the NPR does not include clinical measures (e.g., symptom severity), which could potentially have influenced the magnitude of the associations. Finally, we were not able to investigate other informative outcomes, such

as absenteeism from school, and we did not have access to other measures of the educational system as the so-called *Komvux*, the Swedish educational system for adults, which allows individuals to re-enter to higher educational levels without achieving the previous milestone.

5 CONCLUSIONS

This thesis aimed to study the educational impairment of individuals with SAD and PTSD by using the longitudinal Swedish population registers while controlling for relevant confounders such as comorbidities, cognitive ability, and familial factors. Moreover, a prior validation study of the SAD code employed in the Swedish registers was conducted.

The main conclusions of the thesis can be summarized as follows:

I. The SAD code (F40.1), as recorded in the Swedish National Patient Register, is valid and reliable. The overall severity and functional impairment of the patients with a registered diagnosis of SAD is moderate.

II. SAD is associated with pervasive and substantial decrease in educational attainment across all levels, spanning from compulsory school to postgraduate education, particularly in women. This is over and above psychiatric comorbidities and familial factors shared by siblings.

III. PTSD is associated with pervasive and substantial decreases in educational attainment across all levels, spanning from compulsory school to finishing university. The results were not entirely explained by shared psychiatric comorbidity, general cognitive ability or familial factors.

IV. Examination of the educational attainment of these population-based cohorts of treatment-seeker individuals with SAD and PTSD significantly increases our understanding of the burden and impact associated to these disorders.

V. This new knowledge may help and stimulate initiatives from schools, social services, mental health professionals, and policy-makers to design, implement, and disseminate prevention and intervention programmes for better educational and health policies that can reduce the impact on functioning for those affected with psychiatric disorders.

6 RESUM GLOBAL EN VALENCIÀ

6.1 INTRODUCCIÓ

6.1.1 Trastorns psiquiàtrics d'ansietat, trauma i relacionats amb l'estrès

Els trastorns psiquiàtrics, especialment els trastorns d'ansietat, tenen una alta prevalença arreu del món, i afecten una de cada sis persones als països europeus (OECD, 2018). A més de ser prevalents, comporten una disfuncionalitat elevada i la seua presència repercuteix en el desenvolupament dels individus, però també de les societats, en termes econòmics i socials (Druss et al., 2009).

D'entre tots els trastorns psiquiàtrics, aquesta tesi se centra en el trastorn d'ansietat o fòbia social i el trastorn d'estrès posttraumàtic, que s'expliquen breument a continuació.

6.1.1.1 Trastorn d'ansietat o fòbia social.

- Trets diagnòstics, prevalença, curs i comorbiditat

  El trastorn d'ansietat o fòbia social (FS) té una prevalença vital del 4 % a tot el món, amb xifres que oscil·len entre el 8 i el 12 % en alguns països (Lijster et al., 2017; Ruscio et al., 2008). Tal com es recull en el Manual diagnòstic i estadístic dels trastorns mentals (DSM) i en la Classificació internacional estadística de malalties i problemes relacionats amb la salut (CIM), l'FS es caracteritza per una por o temor exagerat de situacions socials, amb una tendència conductual d'evitació d'aquestes situacions. La por la pot provocar de manera generalitzada qualsevol interacció social o alguna situació en concret, com menjar en públic o parlar amb figures d'autoritat. La por de parlar en públic es considera un subtipus específic del trastorn. Són comuns els símptomes d'hiperactivació, com ara ruboritzar-se, suar o tremolar, els quals poden arribar a ser intensos i induir atacs de pànic (American Psychiatric Association, 2013; World Health Organization, 1993).

  L'FS és més freqüent en dones, sol aparèixer al voltant dels catorze anys i tendeix a ser crònica si no es tracta (Lijster et al., 2017; Steinert et al., 2013; Wittchen et al., 2011). A més a més, fins al 80 % dels casos amb FS solen presentar alguna altra condició psiquiàtrica de manera comòrbida, especialment altres trastorns d'ansietat i trastorns afectius (Fehm et al., 2005; Katzman et al., 2014; B. D. Stein et al., 2017).

- Etiologia

  L'FS es considera un trastorn familiar, ja que els estudis familiars suggereixen que els parents de primer grau de persones amb FS tenen cinc vegades més probabilitats de patir el trastorn que els parents d'individus sans. A més a més, aquest risc augmenta proporcionalment amb el grau de càrrega genètica entre els familiars (Isomura et al., 2015). Igualment, els estudis de bessons i els estudis d'associació de tot el genoma (GWAS, segons l'acrònim en anglès) han confirmat que la contribució dels factors

genètics és rellevant perquè aparega el trastorn (Scaini et al., 2014; M. B. Stein et al., 2017).

Alguns estudis neurobiològics apunten a una hiperactivació del circuit de la por cerebral, el qual inclou l'amígdala, l'ínsula, l'hipocamp i les regions frontoorbitals (Brühl et al., 2014; Fox & Kalin, 2014); així com a disrupcions serotoninèrgiques i de la segregació d'oxitocina (Stein & Andrews, 2015; Ziegler et al., 2015) que s'associen a la presència del trastorn.

Amb referència als factors ambientals, també és substancial la contribució dels factors no compartits amb la família, com poden ser les experiències traumàtiques a l'escola o amb les relacions socials (Fullana et al., 2020). Per altra banda, els factors ambientals compartits amb la família, com l'estatus socioeconòmic o el nombre de germans, tenen menys pes en l'etiologia de l'FS (Isomura et al., 2015; Scaini et al., 2014).

- Tractament

  La teràpia cognitivoconductual (TCC) i els inhibidors selectius de la recaptació de serotonina (ISRS) són les intervencions provades per a tractar l'FS. Altres teràpies psicològiques que s'han fet servir per a l'FS són la psicoteràpia psicodinàmica, la psicoteràpia interpersonal i el *mindfulness* (Mayo-Wilson et al., 2014; Salzer et al., 2018), així com la TCC per internet (Hedman et al., 2011; Nordh et al., 2017).

6.1.1.2 Trastorn d'estrès posttraumàtic

- Trets diagnòstics, prevalença, curs i comorbiditat

  El trastorn d'estrès posttraumàtic (TEPT) és un trastorn psiquiàtric que es dona en aproximadament una tercera part de les persones que han viscut, testimoniat o escoltat la història d'una experiència traumàtica (American Psychiatric Association, 2013). Estar exposat a esdeveniments traumàtics és comú, amb xifres al voltant del 70 % dels adults que respongueren l'enquesta de salut mental de l'Organització Mundial de la Salut (OMS) (Benjet et al., 2016). Cal tenir present que no tots els successos traumàtics tenen la mateixa probabilitat de provocar un TEPT, però la violació, la tortura i la participació en combats armats tenen més risc de desencadenar el desenvolupament del trastorn (Kessler et al., 2017). La prevalença vital mundial és del 5,6 % entre els individus exposats a un esdeveniment traumàtic i del 3,9 % en la població general (Koenen et al., 2017). El TEPT se sol desenvolupar durant el mes següent d'haver patit un esdeveniment traumàtic i es caracteritza per quatre grups de símptomes: reexperimentació del trauma (a través de malsons, *flashbacks*...), evitació persistent d'aspectes que recorden el trauma, alteracions negatives de l'humor i la cognició (conductes autodestructives, anhedonia, cognicions negatives sobre un mateix, els altres o el món) i estat d'alerta (*arousal*) elevat (problemes de concentració, trastorns de la son, irritabilitat, agitació). A més a més, la dissociació i el retraïment emocional són

respostes comunes que caldrà considerar per a planificar el tractament (American Psychiatric Association, 2013).

Habitualment, el TEPT sol aparèixer més tard que altres trastorns d'ansietat o afectius, amb una edat mitjana de 26,6 anys (Lijster et al., 2017). També, entre el 75-80 % dels individus amb un TEPT presenta algun altre trastorn psiquiàtric comòrbid, com pot ser l'abús de substàncies i els trastorns afectius o d'ansietat, i un risc més elevat de suïcidi (Gradus, 2018; Gradus et al., 2015).

- Etiologia

  L'etiologia del TEPT respon a una interacció entre els factors de risc pretrauma, peritrauma i posttrauma (Auxemery, 2012). Segons la literatura científica, la contribució genètica al trastorn és complexa, ja que influeix tant en l'exposició en si a esdeveniments traumàtics (tenir més probabilitats de participar en situacions de violència o combat) com en la pròpia vulnerabilitat de desenvolupar el trastorn després de viure un esdeveniment traumàtic (Afifi et al., 2010; Lebois et al., 2016). Els estudis en bessons estimen l'heretabilitat de la vulnerabilitat genètica en un 49 %, i els estudis GWAS han trobat que el trastorn pot tenir un risc poligènic (Gelernter et al., 2019; Nievergelt et al., 2019).

  Hi ha estudis neurobiològics que apunten a algunes condicions com a factors de risc (hipocamp més menut, major variabilitat del ritme cardíac...), mentre que alguns factors neuroendocrins i neuroinflamatoris en els individus amb TEPT semblen donar-se com a conseqüència de la vivència traumàtica (com la hiperactivació de l'eix Hipotalàmic-hipofisiari-adrenal o HHP, per exemple) (Pitman et al., 2012; Shalev et al., 2017; Xue-Rong et al., 2018).

  Amb referència als factors ambientals, s'ha demostrat que s'associen al TEPT alguns factors sociodemogràfics, com el fet de ser dona, pertànyer a algunes ètnies concretes o tenir un estatus socioeconòmic baix. Així, també relacionats amb l'experiència en si, una major gravetat de l'esdeveniment traumàtic viscut o una major acumulació d'aquests esdeveniments tenen un paper fonamental en la probabilitat de desenvolupar el trastorn (Tortella-Feliu et al., 2019).

- Tractament

  Com a psicoteràpia, la TCC es considera el tractament de primera línia. També s'ha comprovat la TCC basada en el trauma, la teràpia d'exposició prolongada i la teràpia cognitiva per al TEPT (Katzman et al., 2014; National Guideline Alliance, 2018). En casos més particulars, com el d'adults amb un TEPT de més de 3 mesos d'evolució i quan el trauma no ha involucrat la participació en combat, la teràpia de reprocessament i dessensibilització de moviments ràpids (EMDR, de les sigles en anglès) és efectiva. També ho són la teràpia narrativa i la teràpia eclèctica breu (Guideline Development

Panel for the Treatment of PTSD in Adults, 2019). En el cas de la TCC per internet, sols es recomana quan el risc d'autolesió és baix. Ben al contrari, el debrífing hi està contraindicat (National Guideline Alliance, 2018). Com a tractament farmacològic, les guies avalen els antidepressius com la fluoxetina, la paroxetina, la sertralina i la venlafaxina (Katzman et al., 2014; National Guideline Alliance, 2018).

6.1.2 Funcionalitat: adaptació i interferència

El funcionament adaptatiu és un requisit per a una vida autònoma i plena i determina la qualitat de vida dels individus (Aderka et al., 2012). Moltes persones amb trastorns psiquiàtrics en veuen alterada la funcionalitat, fins al punt que la interferència funcional, que pot aparèixer fins i tot abans que la simptomatologia en concret es manifeste (Winters et al., 2005), es considera part dels criteris diagnòstics d'aquest tipus de trastorns (American Psychiatric Association, 2013).

Amb l'objectiu d'avaluar la interferència funcional i així guiar les decisions clíniques dels professionals, l'Organització Mundial de la Salut (OMS) va crear la Classificació internacional del funcionament, la discapacitat i la salut (ICF, de les sigles en anglès). Aquesta classificació, que es basa en el model biopsicosocial, mesura 47 dominis, incloent-hi l'escolar i el social, i ofereix un marc comú de classificació que permet comparar la interferència funcional de les diferents malalties (World Health Organization, 2001). Per altra banda, el DSM també va decidir millorar l'avaluació de la funcionalitat dels trastorns i en l'última actualització incorpora l'escala dissenyada per l'OMS, la WHODAS 2.0 (WHO Disability Assessment Scheduled 2.0) (Ustün et al., 2010), la qual, basant-se en l'ICF, ofereix una avaluació completa del deteriorament global i la funcionalitat.

La prevenció i la intervenció precoç sobre la interferència funcional no sols té una repercussió en la qualitat de vida individual, sinó també en l'eficiència de les societats en general. Una conseqüència de gran rellevància dels trastorns psiquiàtrics és el cost econòmic associat, tant en costos directes i indirectes com en els anomenats d'oportunitat. Els costos directament associats al sistema sanitari i social s'estimen en un 4 % (més de 600 bilions d'euros) del producte interior brut (PIB) arreu dels 28 països de la Unió Europea. Així també els costos indirectes, com els relacionats amb les tasques de cura, conjuntament amb els costos d'oportunitat, referents a la interferència en el nivell educatiu o a tenir menys oportunitats laborals per causa del trastorn, constitueixen un 1,6 % del PIB (240 bilions d'euros) dels països europeus (OECD, 2018). A més a més, la mortalitat precoç associada als trastorns psiquiàtrics, tant per les conseqüències de salut física com per l'elevat risc de suïcidi, és elevada. Aquesta mortalitat precoç es reflecteix en l'índex AVAD, o anys de vida ajustats per discapacitat (DALY, en anglès). AVAD són el nombre d'anys perduts a causa de la mala salut, la discapacitat o la mort prematura, i mesura el total de càrrega de la

malaltia. En resum, els trastorns mentals estan entre les malalties amb un índex AVAD elevat, especialment els trastorns depressius i el TEPT (Wittchen et al., 2011).

Com que aquesta tesi se centra en l'FS i el TEPT, i la seua possible interferència en el rendiment acadèmic, en el pròxim apartat s'explica breument la interferència causada per aquests trastorns.

6.1.2.1 Interferència funcional en FS i TEPT

La interferència funcional en ambdós trastorns és notable. En el cas de l'FS, més del 90% de les persones afectades informen de interferència psicosocial (Leichsenring & Leweke, 2017), amb una associació lineal entre la severitat del trastorn i els diferents indicadors de disfuncionalitat (Fehm et al., 2005; Stein & Kean, 2000). L'indicador més afectat és el social, ja que constitueix un dels símptomes del mateix trastorn i es tradueix en un nombre menor d'amics per als individus amb FS (Gazelle & Rubin, 2019). A més, els individus amb FS solen tenir problemes a l'escola i poden abandonar-la prematurament (Van Ameringen et al., 2003), cosa que n'afecta la futura inclusió laboral. De fet, la desocupació és un ferm predictor de la persistència de l'FS al llarg de la vida adulta (American Psychiatric Association, 2016).

De la mateixa manera, el TEPT també s'ha relacionat amb la interferència funcional en tots els dominis, inclosos el familiar i el de les relacions socials properes, les quals semblen conservar-se més bé en l'FS (Aderka et al., 2012; Birkley et al., 2016; Olatunji et al., 2007). A banda de la disfuncionalitat laboral freqüent, que arriba en alguns casos a una incapacitat total de retornar a la feina després de l'experiència traumàtica (Wald & Taylor, 2009), són rellevants les conseqüències de salut física associades al TEPT, com ara un risc major de malalties cardiovasculars i d'infeccions (Fang et al., 2019; Song et al., 2019).

Però, atès que els estudis d'aquesta tesi es focalitzen en el rendiment educatiu dels individus amb FS o TEPT i que l'educació, com a dret fonamental i universal (UN, 1948), està en la base del desenvolupament de les societats avançades i del benestar de la ciutadania (Lochner, 2004; OECD, 2001), a continuació resumim una introducció a la literatura sobre la interferència en el rendiment educatiu dels individus amb FS o TEPT.

- <u>FS i rendiment educatiu:</u>

  L'FS s'associa a un mal rendiment educatiu, un abandonament escolar precoç i una interferència a l'escola, deguts en part a la por dels individus de parlar en públic, de demanar ajuda als mestres o a l'elevat absentisme escolar derivat del trastorn (Beidel et al., 1999). En alguns estudis, com l'Epidemiologic Catchment Area (Davidson et al., 1994), els adults amb FS o símptomes d'FS referien notes més baixes, repetició de cursos i expulsions freqüents de l'escola, en comparació amb individus de la mateixa

edat sense els símptomes. L'Ontario Health Survey Mental Health Supplement mostrà que el 38,1% dels casos d'FS no acabaren l'institut, en comparació amb el 30,1% dels individus sense el trastorn (Stein & Kean, 2000). També, en un estudi amb 2.128 estudiants suecs d'entre 12 i 14 anys que emplenaren un qüestionari d'ansietat social, s'identificaren 93 casos d'FS, el 91,4% dels quals referiren interferència escolar (Gren-Landell et al., 2009).

- TEPT i rendiment educatiu

  El TEPT i els seus símptomes també s'associen amb un rendiment acadèmic baix, que en part s'explica per una correlació genètica negativa entre ambdues variables (Polimanti et al., 2019). Hi ha estudis de veterans amb TEPT els quals refereixen una interferència acadèmica moderada (Morissette et al., 2019), i estudis d'estudiants universitaris exposats a trauma que també refereixen menor rendiment acadèmic en comparació a aquells estudiants que, malgrat haver estar exposats, no desenvoluparen el trastorn (Boyraz et al., 2016; Pereira et al., 2018). Aquesta associació es manté fins i tot en les estudiants que havien patit una agressió sexual, les quals aconseguien pitjors notes que les que no havien patit un episodi d'agressió sexual (Jordan et al., 2014). L'Early Childhood Longitudinal Study, amb 3.387.565 estudiants de 5è grau, va concloure que els símptomes de TEPT predeien qualificacions més baixes en lectura, matemàtiques i ciència (Goodman et al., 2012). En un altre estudi sobre una mostra representativa d'àmbit estatal, el 38,11% d'adults joves que referien trauma en la infància tenien més del doble de probabilitats d'abandonar l'institut en comparació amb els joves no exposats a trauma (Porche et al., 2011). Finalment, en una enquesta per internet a estudiants universitaris, els que referien TEPT junt amb l'abús d'alcohol reportaven menys rendiment educatiu i més percentatge d'abandonament de la universitat en comparació amb els estudiants sense TEPT o sense consum d'alcohol (Bachrach & Read, 2012).

  En resum, tant l'FS com el TEPT tenen una interferència notable en l'àrea educativa. Els estudis sobre aquest camp realitzats prèviament, tot i ser valuosos, tendien a incloure-hi mostres menudes, empraven dissenys transversals, exploraven els trastorns d'ansietat o d'estrès com a grups generals, utilitzaven mesures d'autoinformes, no hi incloïen grups control de no exposats al trastorn, no controlaven per factors de confusió (com els factors familiars o les comorbiditats psiquiàtriques) o estaven exclusivament focalitzats en un grup d'edat o nivell educatiu.

  Per a explorar l'associació entre l'FS o el TEPT i el rendiment educatiu tenint presents les limitacions enumerades i controlant per factors familiars, comorbiditats psiquiàtriques i altres variables rellevants com la capacitat cognitiva general, vam dissenyar dos estudis longitudinals de cohorts poblacionals amb dades educatives objectives compilades de manera prospectiva. Les dades per a aquests estudis s'extragueren dels registres administratius de Suècia, els quals recullen informació

administrativa i de salut de tots els ciutadans del país, i que es descriuen en l'apartat següent.

6.1.3 Registres poblacionals a Suècia

És comú en molts països elaborar registres longitudinals que inclouen informació demogràfica, social, sanitària o laboral, els quals comprenen tota la població. Els registres sanitaris són essencials per a la salut pública i faciliten la recerca epidemiològica. En el cas de Suècia, són diversos els registres que recopilen informació sobre els ciutadans, i a més, mitjançant el número d'identificació personal de cada ciutadà (anonimitzat per privacitat), és possible creuar les dades dels diferents registres i així obtenir informació de valor epidemiològic de cada individu.

Per a portar a terme els estudis d'aquesta tesi es recopilà informació dels registres següents:

- El Registre total de població (Ludvigsson et al., 2016): reuneix des de 1968 informació sociodemogràfica (sexe, data de naixement, llinatge, migració) de tots els ciutadans suecs. Inclou el Registre migratori, que recull les immigracions i emigracions del país; i el Registre multigeneració, que permet identificar els llinatges biològics i adoptius des de 1932, així com identificar familiars, com ara els germans o els cosins (Ekbom, 2011).
- El Registre nacional de pacients (NPR de les sigles en anglès) (Ludvigsson et al., 2011): inclou informació sobre els diagnòstics clínics formulats per metges especialistes, dades derivades dels ingressos hospitalaris, com les dates d'admissió i d'alta de l'hospital, a més de dades personals, com l'edat, el sexe o el lloc de residència dels pacients. Des de 1973 s'inclou la informació dels dispositius hospitalaris de salut mental, i és a partir de 2001 que s'amplia amb la informació dels serveis ambulatoris, tant públics com privats (exceptuant-ne l'atenció primària). Els diagnòstics estan registrats en l'NPR seguint l'adaptació sueca de les versions vuitena, novena i dècima de la CIM.
- El Registre escolar nacional: inclou informació sobre el rendiment acadèmic de totes les assignatures i de totes les escoles del país. Amb les notes en llengua sueca, llengua anglesa i matemàtiques es determina si l'estudiant reuneix els criteris d'idoneïtat o no per a cursar l'educació secundària superior postobligatòria (The Swedish National Agency for Education, 2018).
- La Base de dades longitudinal sobre seguretat social (LISA, de les sigles en suec): aquest registre, que s'actualitza cada any, conté informació educativa, laboral i social de tots els individus majors de setze anys que resideixen al país (Ludvigsson et al., 2019).
- El Registre de causes i data de la mort (Statistics Sweden, 2013).
- El Registre d'allistament militar: inclou els resultats de l'avaluació física i psicològica (incloent-hi la capacitat cognitiva general) dels individus que feren el servei militar entre 1969 i 2010.

6.1.4 Validació dels codis diagnòstics al Registre nacional de pacients de Suècia

El gran potencial dels registres suecs per a investigar factors de risc i conseqüències associades als trastorns psiquiàtrics està lligat a la fiabilitat i validesa dels mateixos codis que s'utilitzen per a registrar els diagnòstics (Rosén, 2002). Darrerament, s'han fet molts estudis de validació de malalties somàtiques i psiquiàtriques, tots amb bons valors predictius positius (PPV), i per tant bona validesa (Ludvigsson et al., 2011; Rück et al., 2015).

En el cas d'aquesta tesi, el codi diagnòstic de TEPT segons la CIM (versió sueca) per a l'NPR va ser prèviament validat, amb un 84% (PPV=0.84 [95% CI 0.79-0.9) dels casos avaluats complint criteris per a TEPT segons el DSM-IV (Hollander et al., 2019). En canvi, els codis diagnòstics dels trastorns d'ansietat, i en particular de l'FS, restava per validar.

6.2 OBJECTIUS D'AQUESTA TESI

L'objectiu global d'aquest projecte va ser investigar l'associació entre FS i TEPT i el rendiment acadèmic.

I. Estudi I: examinar la validesa i la fiabilitat del codi de la CIM-10 d'FS registrat en l'NPR. Aquest estudi es va dissenyar com a prerequisit per a portar a terme l'Estudi II amb garanties.
II. Estudi II: explorar l'associació entre l'FS i el rendiment acadèmic al llarg de la vida dels individus, per mitjà d'un estudi de cohorts de la població sueca.
III. Estudi III: explorar l'associació entre el TEPT i el rendiment acadèmic al llarg de la vida dels individus, emprant l'estudi de cohorts de la població sueca.

6.3 ESTUDIS DE RECERCA

6.3.1 Validació del codi de la CIM-10 per fòbia social en el Registre nacional de pacients de Suècia

6.3.1.1 Introducció i objectiu.

Com que els registres ofereixen àmplies possibilitats de recerca epidemiològica, explorar la validesa i fiabilitat dels codis diagnòstics que contenen és essencial. Malgrat que molts codis de malalties somàtiques i psiquiàtriques s'havien validat prèviament, aquest no era el cas de l'FS. Per tant, tenint present que a Suècia es registren més de tres mil casos d'FS a l'any, vam dissenyar un estudi per a validar el codi F40.1 de la CIM-10 mitjançant la revisió d'històries clíniques.

6.3.1.2 Resum dels mètodes

Després d'obtenir l'aprovació del projecte per part del comitè ètic, l'Agència de Salut i Benestar de Suècia ens proporcionà una mostra aleatòria de 300 números d'identificació personal que presentaven un diagnòstic d'FS registrat a l'NPR. Una vegada localitzades les històries clíniques dels individus arreu dels centres mèdics de

tot el país, les sol·licitàrem per correu postal. Rebérem 117 històries clíniques, les quals van ser revisades per dos psicòlegs clínics o psiquiatres de manera independent. Els jutges havien d'emplenar una taula per decidir si la informació que contenia la història clínica acomplia criteris de diagnòstic d'FS (seguint la CIM-10 i el DSM-IV-TR). Si hi havia desacord, un tercer jutge establia el millor diagnòstic. Es van excloure 22 arxius per no contenir suficient informació per a ser valorats. Les mesures de PPV i κappa de Cohen (per a obtenir la fiabilitat entre jutges) es calcularen. Quan no satisfeien els criteris d'FS, es demanava als jutges els diagnòstics alternatius més plausibles. A més a més, les escales Clinical Global Impression – Severity (CGI-S) i la Global Assessment of Functioning (GAF) es van emplenar en cada història clínica per a avaluar la gravetat dels símptomes, així com el funcionament global de la mostra de casos. El coeficient de correlació intraclasse es va utilitzar per a calcular l'acord entre jutges.

6.3.1.3 Resum dels resultats

De les 95 històries clíniques incloses en les anàlisis, el 81,05 % (77 casos) es van avaluar com a vertaders positius (els pacients complien criteris diagnòstics d'FS) (PPV = 0,81 [95 % CI 0,72-0,88]), mentre que els 18 restants es van considerar falsos positius (malgrat tenir el codi diagnòstic, la informació de la història clínica no indicava que s'acompliren criteris diagnòstics d'FS). La concordança entre jutges va ser substancial (κ= 0,72) i els diagnòstics alternatius més freqüents que proposaven els jutges van ser altres trastorns d'ansietat, depressió i trastorns de l'espectre autista. Les escales CGI-S i GAF indicaren que la mostra de pacients avaluada tenia una interferència funcional moderada, amb una concordança entre jutges moderada per a la CGI-S (ICC = 0,72 [95 % CI, 0,54-0,82]) i bona per a la GAF (ICC=0,82 [95 % CI, 0,71-0,89]).

6.3.1.4 Conclusió

El codi d'FS de la CIM-10 utilitzat a l'NPR és en general vàlid i fiable. La majoria de pacients presentaven una interferència funcional moderada, per la qual cosa els resultats són generalitzables, especialment en persones amb el trastorn que acudeixen als serveis sanitaris en cerca de tractament.

6.3.2 Estudis II i III. L'associació de la fòbia social i el trastorn d'estrès posttraumàtic amb el rendiment acadèmic

6.3.2.1 Introducció i objectiu.

Tant l'FS com el TEPT s'han associat al baix rendiment acadèmic, però els estudis previs tenien limitacions metodològiques. Per mitjà d'estudis observacionals de cohorts poblacionals avaluarem l'associació entre FS (Estudi II) i TEPT (Estudi III) amb indicadors objectius de rendiment acadèmic de tot el cicle escolar, comparant-los amb la població general però també amb els germans lliures de trastorns.

6.3.2.2 Resum dels mètodes

Després de l'aprovació del Comitè Ètic, i mitjançant els registres poblacionals nacionals suecs, es va dissenyar una cohort que incloïa tots els individus que no foren bessons nascuts a Suècia entre 1973 i 1997, als quals se'ls va fer un seguiment fins al 31 de desembre de 2013.

Tots els individus amb un diagnòstic d'FS (F40.1) a l'NPR van considerar-se exposats a l'Estudi II. Per a l'Estudi III, se seleccionaren aquells individus amb TEPT (F43.1) diagnosticats abans de l'edat esperable d'acabament del nivell educatiu estudiat (per exemple, per a avaluar la finalització de l'escola secundària superior, es consideraren exposats els individus diagnosticats abans dels 19 anys d'edat).

Per tal d'assegurar que tots els individus foren vius, no hagueren emigrat de Suècia i foren prou grans per haver tingut temps de cursar el nivell educatiu analitzat, es dissenyaren 5 subcohorts diferents, una per cada nivell educatiu estudiat, de la següent manera (la representació gràfica de les subcohorts es pot visualitzar en la **Figura 1,** a la pàgina 37):

Educació obligatòria (la informació educativa per a les anàlisis es va extraure del Registre nacional escolar):

a. Idoneïtat (requisits) per accedir a l'educació secundària no obligatòria (15-16 anys d'edat): individus que es graduaren (o no) de l'educació obligatòria entre 1998 i 2013 i no havien mort o emigrat de Suècia abans dels 15 anys d'edat. Per a l'Estudi II, s'utilitzà també aquesta cohort per a explorar les assignatures de l'últim curs de l'educació obligatòria, categoritzades de manera binària, si s'aprovaven o no.

Educació postobligatòria (la informació educativa per a les anàlisis en els nivells postobligatoris es va extreure del LISA):

a. Finalització (o no) de l'educació secundària superior: individus nascuts entre 1973 i 1994 i que no havien mort o emigrat de Suècia abans dels 19 anys d'edat. El rang d'edat en acabar el seguiment (2013) era entre 19 i 40 anys.
b. Iniciació (o no) d'estudis universitaris: individus nascuts entre 1973 i 1992 i que no havien mort o emigrat de Suècia abans dels 21 anys d'edat. El rang d'edat en acabar el seguiment (2013) era entre 21 i 40 anys.
c. Finalització (o no) d'un grau universitari: individus nascuts entre 1973 i 1988 i que no havien mort o emigrat de Suècia abans dels 25 anys d'edat. El rang d'edat en acabar el seguiment (2013) era entre 25 i 40 anys.
d. Finalització (o no) d'estudis de postgrau (sols utilitzat a l'Estudi II): individus nascuts entre 1973 i 1983 i que no havien mort o emigrat de Suècia abans dels 30 anys d'edat. El rang d'edat en acabar el seguiment (2013) era entre 30 i 40 anys.

- Covariants

  En un intent de controlar per variables amb possible efecte confusor de l'associació sota estudi, es van utilitzar variables demogràfiques extretes del Registre de població total (com sexe, any de naixement i edat parental en el moment de naixement de l'individu) per als ajustaments de les anàlisis.

  De l'NPR es van identificar, per a cada cohort, aquells individus amb diagnòstic d'algun trastorn psiquiàtric comòrbid al llarg de la vida. Aquests trastorns s'agruparen de la següent manera:

  - Trastorns del neurodesenvolupament (trastorns de l'espectre autista, trastorn de dèficit d'atenció i hiperactivitat, síndrome de La Tourette i trastorn per tics crònics i dificultats de l'aprenentatge).
  - Trastorn de conducta (sols per a l'Estudi III).
  - Trastorns fòbics, d'ansietat, obsessivocompulsiu i relacionats amb l'estrès (excloent FS en l'Estudi II i el grup relacionat amb l'estrès en l'Estudi III).
  - Trastorns de la conducta alimentària (sols per a l'Estudi III).
  - Trastorns psicòtics (esquizofrènia, trastorn esquizotípic i trastorn delirant).
  - Trastorns afectius (trastorn bipolar, depressió i trastorn persistent de l'humor).
  - Trastorns per abús de substàncies.

  En l'Estudi III, per a explorar l'associació descrita en la literatura prèvia sobre el fet que un nivell d'intel·ligència baix podia ser un factor de risc per al TEPT, vam emprar el Registre d'allistament militar per seleccionar una submostra d'homes nascuts a Suècia entre 1973 i 1997, que comptaven amb mesures de capacitat cognitiva general avaluades durant l'allistament militar als 18 anys d'edat.

- Anàlisi de dades

  Es van analitzar les dades mitjançant models de regressió logística, que van oferir els resultats en forma d'odds ratios (OR) amb els corresponents intervals de confiança (IC) del 95 %, per comparar els individus exposats (individus amb FS o TEPT) amb els no exposats als trastorns, en relació amb totes les variables educatives sota estudi (dicotòmiques).

  En primer lloc, es van comparar les persones exposades (els individus amb FS i TEPT, respectivament) amb controls no exposats de la població general. Aquesta comparació es va dur a terme en cada subcohort. Primer es van realitzar les anàlisis crues. En un segon pas, aquestes anàlisis es van ajustar per sexe, any de naixement i edat d'ambdós pares al moment de naixement, resultant en les OR ajustades [aOR].

  En segon lloc, per a controlar les possibles variables confusores existents dins d'una mateixa família, els individus exposats es van comparar amb els seus germans biològics de pare i mare no afectats per les malalties. Aquest disseny de comparar amb els

germans permet controlar certs factors genètics, així com factors ambientals comuns en els pares, com per exemple la psicopatologia, la història de malalties o l'estatus socioeconòmic. Aquesta comparació es va dur a terme en cada subcohort i també es va ajustar per les variables enumerades en l'apartat anterior.

En tercer lloc, per a explorar si les condicions psiquiàtriques comòrbides comunes a l'FS o al TEPT podien afectar l'associació, vam realitzar anàlisis addicionals a partir dels quals es van excloure, de manera sistemàtica, aquelles persones amb subgrups de trastorns comòrbids a l'FS i al TEPT. Aquestes anàlisis es va dur a terme en cada subcohort i també van ser ajustades per sexe, any de naixement i edat dels pares.

Finalment, per a l'Estudi III, seleccionant una submostra d'homes que participaren en l'allistament militar, es van repetir les anàlisis ajustant pel nivell d'habilitat cognitiva general. De manera suplementària, també es van repetir les anàlisis principals de comparació amb el total de la població, ajustant per haver superat (o no) el nivell educatiu antecedent. També, adicionalment, es van repetir les anàlisis ajustant per totes les condicions psiquiàtriques comòrbides alhora.

6.3.2.3 Resum dels resultats

- Estudi II

  Dels 2.238.837 individus nascuts a Suècia inclosos en la cohort, 15.755 van rebre un diagnòstic d'FS. La proporció de dones en el grup d'FS va ser significativament major (8.706; 55,3%) que en el grup no exposat (1.081.036; 48,7%).
  A partir de la cohort inicial, es van avaluar 1.425.340 individus per finalitzar l'educació obligatòria (10.093 amb FS), 1.998.971 per finalitzar l'educació secundària superior (14.997 amb FS), 1.794.981 per iniciar estudis universitaris (13.901 amb FS), 1.356.841 per finalitzar una carrera universitària (10.731 amb FS) i 899.325 per acabar la formació de postgrau (6.680 amb FS).

  Comparat amb els individus no exposats, els individus diagnosticats amb FS van ser menys propensos a aprovar totes les assignatures en l'últim any d'educació obligatòria (OR ajustada [aOR] amb rang de 0,19 a 0,44) i tenien menys probabilitat de tenir la idoneïtat per a cursar un programa d'educació secundària superior. En concret, els individus amb FS tenien un 69% menys probabilitat de cursar un programa vocacional (aOR=0,31 [95 % CI, 0,30–0,33]) i un 48% menys probabilitat de cursar-ne un acadèmic (aOR=0,52 [95 % CI, 0,50–0,55]), 81% menys probabilitat d'acabar l'educació secundària superior (aOR=0,19 [95 % CI, 0,19–0,20]), 53% menys probabilitat d'iniciar estudis universitaris (aOR=0,47 [95 % CI, 0,45–0,49]), 65% menys probable que finalitzen una carrera universitària (aOR=0,35 [95 % CI, 0,33–0,37]) i 42% menys de probabilitat de finalitzar l'educació terciària de postgrau

(aOR=0,58 [95 % CI, 0,43–0,80]). Les dones van presentar un pitjor rendiment que els homes en tots els nivells estudiats –excepte en els estudis de postgrau.

En la comparació amb els germans, els resultats es van mantenir encara que es van atenuar (aOR entre 0,31 i 0,63). Quan es van repetir les anàlisis excloent els grups de comorbiditats psiquiàtriques, els resultats tampoc van canviar significativament.

- Estudi III

  De la cohort inicial de 2.244.193 individus (48,7% dones), se'n van avaluar 1.425.326 per finalitzar l'educació obligatòria (919 amb TEPT previ), 2.001.944 per finalitzar l'educació secundària superior (2.013 amb TEPT previ), 1.796.407 per iniciar estudis universitaris (2.243 amb TEPT previ) i 1.356.841 per finalitzar una carrera universitària (2.254 amb TEPT previ).

  Comparat amb els individus no exposats, els individus diagnosticats amb TEPT prèviament a la finalització del nivell educatiu estudiat tenien un 82% menys de probabilitat de tenir la idoneïtat per a cursar l'educació secundària superior (aOR=0,18 [95 % CI, 0,15–0,20]), un 87% menys de probabilitat d'acabar l'educació secundària superior (aOR=0,13 [95 % CI, 0,12–0,14]), un 68% menys de probabilitat d'iniciar estudis universitaris (aOR=0,32 [95 % CI, 0,28–0,35]) i un 73% menys de probabilitat de finalitzar una carrera universitària (aOR=0.27 [95 % CI, 0,23–0,31]). No hi va haver diferències significatives entre sexes.

  En la comparació amb els germans, els resultats van romandre significatius però es van atenuar fins a quasi la meitat (rang d'aOR de 0,22 a 0,53). L'exclusió dels grups de les comorbiditats psiquiàtriques més freqüents del TEPT, i la repetició de les anàlisis ajustant per haver completat el nivell educatiu anterior a l'estudiat o per la capacitat cognitiva general, l'associació no es va veure significativament alterada.

6.3.2.4 Conclusions principals

Els individus amb FS, especialment les dones, i en comparació amb la població general, tenien menys probabilitat d'aprovar totes les assignatures de l'escola obligatòria, així com de superar tots els nivells educatius estudiats, des de l'educació obligatòria fins a la terciària, incloent-hi estudis de postgrau.

Els individus amb TEPT diagnosticats abans d'acabar el nivell educatiu tenien menys probabilitat de superar tots els nivells educatius estudiats, des de l'educació obligatòria fins a la finalització d'estudis universitaris, comparats amb la població general.

Els resultats es mantingueren, malgrat veure's atenuats, després de controlar per factors familiars en la comparació amb els germans, cosa que suggereix que alguns factors familiars compartits poden ser rellevants per a explicar part de l'associació entre l'FS o

el TEPT i el rendiment acadèmic. Quan es tingueren en compte els trastorns psiquiàtrics comòrbids (i haver superat el nivell educatiu anterior així com la capacitat cognitiva general en l'Estudi III), els resultats es mantingueren sense gaire canvis.

6.4 DISCUSSIÓ

Atès a la marcada interfèrencia funcional de l'FS i el TEPT, aquesta tesi pretén explorar l'associació entre aquests trastorns i el rendiment acadèmic al llarg de la vida.

De l'estudi de validació s'obtenen les garanties de validesa i fiabilitat del codi diagnòstic d'FS de la CIM-10 utilitzat a l'NPR, el qual obtigué valors similars a la validesa i fiabilitat del codi de TEPT descrita per Hollander *et al.* (2019). A més a més, es va veure que la majoria de pacients amb FS presentaven una interferència funcional moderada, per la qual cosa els resultats són generalitzables, especialment en persones amb el trastorn que acudeixen als serveis sanitaris en cerca de tractament.

Els resultats dels Estudis II I III d'aquesta tesi mostren que ambdós trastorns s'associen de manera consistent a un rendiment acadèmic baix al llarg de tots els nivells educatius. Per a l'FS, especialment per a les dones, la menor probabilitat de superar cada nivell oscil·lava entre el 42% i el 81% segons el nivell acadèmic, i per al cas de TEPT, la menor probabilitat se situava entre el 68% i el 87%, en comparació amb la població general i sense diferències significatives entre sexes.
Cal destacar que el nivell amb major dificultat és l'educació secundària superior (el batxillerat, en el sistema educatiu espanyol), en què el 81% dels individus lliures de trastorns completaven el nivell, en comparació amb el 46% dels individus amb FS i sols el 33% dels individus amb TEPT. Aquest nivell és d'especial rellevància, ja que no superar-lo s'associa a més dificultat per a cursar estudis universitaris, més dificultat per aconseguir i mantenir una feina i, per als homes, més probabilitat de baixes laborals (Hoff et al., 2018).

Relacionat amb les variables amb possible efecte confusor de l'associació entre la presència d'FS o TEPT i el rendiment acadèmic, l'exclusió de diferents grups de trastorns comòrbids (un grup de trastorns en cada pas) no va alterar els resultats, tot i que la presència de comorbiditat psiquiàtrica dels individus amb FS o TEPT era de més del 83%, en contraposició amb la presència de comorbiditat psiquiàtrica dels individus lliures d'aquests trastorns, la qual era de menys del 14%. En el cas del TEPT, repetir les anàlisis excloent-ne tots els trastorns comòrbids alhora o ajustar-les per haver superat o no el nivell educatiu anterior, va atenuar l'associació entre el trastorn i el menor rendiment educatiu, però no la va alterar. Així també, les anàlisis ajustades per la capacitat cognitiva general realitzades en la submostra d'homes que havien realitzat el servei militar mostraren que, malgrat els homes amb diagnòstic de TEPT presentaven una menor capacitat cognitiva general en comparació amb aquells que no tenien TEPT, els homes amb TEPT seguien mostrant una menor probabilitat de finalitzar els nivells

educatius (a excepció de l'inici de la universitat), indicant que l'associació entre el TEPT i el menor rendiment educatiu sembla independent del nivell de capacitat cognitiva de l'individu.

En la comparació amb els germans, on es tenen en consideració els factors genètics i ambientals compartits (com ara el nivell educatiu dels pares o l'estil parental), els individus amb FS o TEPT mantenien un pitjor rendiment comparat amb el dels seus germans no afectats, si bé és cert que la menor probabilitat de finalitzar els nivells no era tan marcada com quan es comparaven amb la població general.
Això va ser així tant per a l'FS com per al TEPT, en què la menor probabilitat es va veure reduïda a la meitat, la qual cosa indica que certs factors compartits entre germans, com la història de malalties o d'educació dels pares o l'estatus socioeconòmic o genètic —que en el cas de TEPT s'ha vist per ell mateix associat a un menor rendiment acadèmic (Polimanti et al., 2019; Rimfeld et al., 2018; Shakeshaft et al., 2013) —, poden influir en l'associació entre el rendiment acadèmic i els trastorns, però que així i tot, tant l'FS com el TEPT en si, continuen tenint un pes important en l'associació.

Malgrat que molts altres factors poden tenir una influència en l'associació entre els trastorns estudiats i el rendiment acadèmic, tenint presents els resultats dels dos estudis d'aquesta tesi, se suggereix que la presència d'FS o TEPT per si mateixos és un important predictor de rendiment acadèmic baix, independentment de la genètica i l'ambient compartits. Aquesta troballa confirma la impressió clínica i reforça i amplia la relació descrita a alguns estudis previs. Malgrat això, caldrà explorar si la genètica o l'ambient no compartits pot explicar part de la variància de les associacions descrites.

6.4.1.1 Comparació amb estudis epidemiològics similars.

Tenint present la literatura prèvia que ha pretès avaluar la relació entre altres trastorns psiquiàtrics i el rendiment educatiu amb una metodologia similar, així com les impressions clíniques, és clar que el mateix patró de rendiment acadèmic baix està associat a molts altres trastorns psiquiàtrics. Els nostres resultats són comparables als trobats per Dalsgaard et al (2020), on les persones amb un trastorn mental tenien una menor probabilitat (0.52; 95% CI, 0.52-0.53) de realitzar l'examen del final de l'escola obligatòria (comparable a la idoneïtat del nostre estudi) en comparació amb les persones sense trastorn mental (0.88; 95%CI, 0.88-0.88) (Dalsgaard et al., 2020). Així i tot, l'estudi no contemplava el TEPT, i l'FS estava inclosa al grup dels trastorns d'ansietat, pel que el nostre estudi completa l'associació descrita amb les dues condicions per separat.

Tenint present la baixa especificitat entre els trastorns psiquiàtrics i deixant de banda algunes diferències metodològiques entre els estudis, sembla que els individus amb diagnòstic de TEPT i, en menor proporció, els individus amb diagnòstic d'FS, presenten un risc més elevat de no completar els nivells educatius en comparació amb

altres trastons psiquiatrics, per exemple el trastorn obsessivocompulsiu (TOC) o la síndrome de La Tourette o de trastorn per tics complexos (Pérez-Vigil, Fernández de la Cruz, Brander, Isomura, Jangmo, Feldman, et al., 2018; Pérez-Vigil, Fernández de la Cruz, Brander, Isomura, Jangmo, Kuja-Halkola, et al., 2018). Focalitzant-nos en la finalització de l'educació secundària superior com a referència, els resultats d'aquests estudis, portats a terme en la mateixa població que els nostres, es compararien de la següent manera: la probabilitat de finalitzar la secundària superior seria un 87% menor per als individus amb un previ TEPT, un 81% menor per als individus amb FS, un 59% menor per als individus amb síndrome de La Tourette o trastorn per tics complexos i un 57% menor per als individus amb TOC.

6.4.1.2 Implicacions clíniques i socials

Els resultats d'aquesta tesi emfasitzen la importància d'adreçar la interferència funcional que es deriva dels trastorns psiquiàtrics, en especial la millora del rendiment acadèmic en individus amb FS i TEPT. Per a pal.liar aquesta disfuncionalitat, és necessari implementar accions per prevenir la salut mental i millorar la qualitat de vida, tant individualment com socialment. En els últims anys s'han dissenyat programes d'intervenció específics, alguns desenvolupats en els mateixos centres educatius (Lereya et al., 2019; OECD, 2018). En una metanàlisi que contemplava 213 programes de prevenció i intervenció sobre la salut mental en les escoles es demostrà que, a més de promoure la salut mental en general, aquests programes també servirien per millorar la possible simptomatologia psiquiàtrica, així com per millorar fins a un 11 % el rendiment acadèmic dels estudiants (Durlak et al., 2011). Una de les raons que explicaria la millora en el rendiment acadèmic és que els individus que tenen dificultats en les etapes primerenques però reben un suport adequat, tenen més probabilitats d'aconseguir nivells educatius superiors, independentment de la situació familiar o social de base (OECD, 2012).

La major part dels programes implementats tenen un caràcter general, i promouen la salut mental i el benestar aplicats de manera universal per a tot l'estudiantat. D'altres es focalitzen en previndre majors conseqüències i intervindre sobre les dificultats o els símptomes psiquiàtrics que ja presenten alguns alumnes.
En relació a les intervencions centrades específicament en els trastorns que ens ocupen, alguns dels programes desenvolupats s'han implementat amb bons resultats (Rolfsnes & Idsoe, 2011; Scaini et al., 2016).

En el cas de l'FS, tenint en compte que la majoria de situacions temudes es presenten en el context escolar (participar en treballs en grup, contestar preguntes a classe, parlar amb figures d'autoritat com els mestres, fer presentacions orals…), l'evitació de les demandes exigides és freqüent. A més, els símptomes d'hiperactivació i les cognicions de baixa capacitat interfereixen en el rendiment acadèmic (Ohayon & Schatzberg, 2010; Van Ameringen et al., 2003). Per tant, és clau implementar intervencions per a

detectar de manera primerenca simptomatologia d'FS, ensinistrant-hi els companys i el personal de l'escola. Un exemple és el programa de cribratge en dos passos per mitjà d'una breu entrevista telefònica, que ha provat ser efectiu (Sweeney et al., 2015). Relacionat amb la intervenció sobre la símptomatologia d'FS, un exemple d'intervenció amb evidència és el 12-week Skills for Academic and Social Success (SASS) programme (Masia Warner et al., 2018), el qual s'ha vist que redueix els símptomes d'ansietat social i millora el funcionament escolar, en comparació amb intervencions de només aconsellament (*counselling*) a l'escola.

En el cas del TEPT, les respostes esperables després d'un esdeveniment traumàtic i els mateixos símptomes del trastorn, com són la reexperimentació, la hiperactivació, la dissociació o els problemes del son, poden interferir en els recursos atencionals i de memòria, i per tant en el rendiment acadèmic (Scott et al., 2015).
Algunes intervencions atenen al fet que dos de cada tres infants tenen probabilitats d'haver patit experiències traumàtiques als 17 anys d'edat amb un percentatge d'aquests que desenvoluparà TEPT, i que l'escola ajuda a recuperar el sentit de seguretat. Hi ha escoles que han adoptat la perspectiva de trauma (*trauma-informed approach*) la qual suposa un canvi de filosofia dels professionals i del centre, més que intervencions específiques (Substance Abuse and Mental Health Services Administration, 2014). En relació amb els programés d'intervenció més aplicats, en una metanàlisi de 19 programes, les intervencions mostraven bons resultats en reduir la simptomatologia del TEPT (Rolfsnes & Idsoe, 2011). Alguns exemples són la *Cognitive Behavioral Intervention for Trauma in Schools* (Hoover et al., 2018; Jaycox et al., 2012), *l' ERASE-Stress programme* (Berger & Gelkopf, 2009) o el *RAP Club* (Mendelson et al., 2015).

Aquest conjunt d'intervencions que milloren la simptomatologia, però també el rendiment acadèmic, té el potencial de reduir també el cost social i econòmic derivat d'ambdues dificultats. Això és així perquè el nivell educatiu prediu la inserció laboral posterior (Shavit & Muller, 1998) i contribueix a reduir l'índex AVAD (Wittchen et al., 2011). En aquesta línia, s'assumeix que les conseqüències de l'FS i el TEPT en l'entorn laboral seran paleses, com ho són amb altres trastorns psiquiàtrics (Gabriel & Liimatainen, 2000; Helgesson et al., 2017; Niederkrotenthaler et al., 2016; Pérez-Vigil et al., 2019) i que intervenir-hi de manera primerenca contribuirà a reduir-ne les disparitats econòmiques i a millorar-ne l'adaptabilitat.

6.4.1.3 Implicacions per a la recerca i direccions futures

En l'última dècada, l'adopció amb l'ICF d'un marc biopsicosocial per a la comprensió de la interferència ha propulsat la creació d'instruments vàlids d'avaluació com la WHODAS (Federici et al., 2017; Ustün et al., 2010) per tal de cobrir una necessitat tant dels professionals com de les institucions. En aquesta línea, han augmentat també els estudis que tenen per objectiu quantificar, de manera regular, el rendiment acadèmic de

la població general arreu del món (OECD, 2019a, 2019b). Més específicament, alguns s'han centrat en el rendiment acadèmic dels individus amb un trastorn psiquiàtric (Dalsgaard et al., 2020; Pérez-Vigil, Fernández de la Cruz, Brander, Isomura, Jangmo, Feldman, et al., 2018; Pérez-Vigil, Fernández de la Cruz, Brander, Isomura, Jangmo, Kuja-Halkola, et al., 2018; Wickersham et al., 2020). En aquest punt, seria de gran utilitat poder determinar els factors que es troben a la base d'aquesta associació. Per exemple, els factors familiars amb possible efecte confusor com són la història previa de malalties en la família, han estat poc contemplats en estudis previs. Poder esclarir les contribucions d'aquests factors en l'associació entre FS i TEPT i un menor rendiment acadèmic pot contribuir a dissenyar estratègies de prevenció més eficients, tant del rendiment acadèmic baix com de la inclusió posterior en el mercat laboral d'aquests individus (Mojtabai et al., 2015).

6.4.1.4 Resum del punts forts principals

El punt fort d'aquests estudis és la utilització dels amplis registres suecs, que inclouen dades de salut i d'educació objectives i representatives d'àmbit nacional, la qual cosa assegura un risc baix de biaixos de selecció, de desitjabilitat social i de memòria. Altres punts forts són que els codis de diagnòstic psiquiàtric utilitzats han estat validats, i que el període de seguiment de més de vint anys permet un temps suficient a les diferents cohorts per a assolir els nivells educatius de la trajectòria acadèmica. Destacable també el disseny quasiexperimental del model de comparació amb germans, que va permetre un control estricte de moltes altres variables confusores, com el 50 % de la càrrega genètica i d'ambient compartit. Per últim, tenir en compte un ampli rang de trastorns psiquiàtrics comòrbids en l'exploració de l'associació també ha contribuit a atorgar una major precisió de l'estimació entre l'FS i el TEPT i el rendiment acadèmic.

6.4.1.5 Resum de les limitacions principals

En l'Estudi I, sols van arribar (i per tant es van poder avaluar) un terç del nombre d'històries clíniques sol·licitades, fet que podria constituir un biaix de selecció. A més a més, els jutges no eren cecs per al diagnòstic, fet que podria haver incrementat el biaix confirmatori de diagnòstics d'FS. Finalment, els jutges emplenaren la CGI-S i la GAF basant-se en la informació de les històries clíniques, sense entrevistar directament els pacients. No es coneix la validesa de les escales emprades d'aquesta manera, per la qual cosa els resultats s'han de considerar com una impressió clínica general de la severitat i el funcionament dels pacients, però, així i tot, la concordança entre jutges va ser adequada per a ambdós instruments.

Per als estudis II i III, un tipus d'error de mesura podria haver estat la classificació errònia dels trastorns de les nostres cohorts. Els casos que inclou l'NPR només es refereixen a persones que han buscat tractament en els serveis sanitaris i han estat diagnosticats per un especialista en medicina; per tant, el nombre de casos amb FS o TEPT en el registre és menor que la prevalença descrita dels trastorns. Això significa

que els pacients inclosos en l'NPR podrien no ser representatius d'aquells pacients amb els trastorns, però que, o bé no busquen ajuda, o bé han estat diagnosticats per professionals no metges o per metges d'atenció primària, informació que el registre no recull. A més, el registre només va començar a incloure pacients diagnosticats o seguits en l'àmbit ambulatori des de l'any 2001, i per tant fins a l'any 2000 només incloïa aquells que havien tingut un ingrés hospitalari; per això, la majoria de casos d'FS i de TEPT reflectits en l'NPR es refereixen als diagnosticats després del 2001, ja que rarament requereixen hospitalització. A més a més, l'NPR no inclou mesures clíniques, com poden ser la gravetat del símptomes, variable que podria haver influït en la magnitud de les associacions al rendiment acadèmic. Aquestes limitacions també s'apliquen a la identificació del trastorns psiquiàtrics comòrbids. Finalment, no va ser possible investigar altres tipus de variables informatives, com l'absentisme escolar o els certificats acadèmics obtinguts a través de l'educació per a adults (Komvux, en suec), sistema que permet accedir de nou al sistema educatiu sense haver completat el nivell anterior.

6.5 CONCLUSIONS

Aquesta tesi té com a objectiu estudiar el rendiment acadèmic dels individus amb FS i TEPT utilitzant les dades dels registres longitudinals de la població sueca, controlant variables confusores de rellevància, com ara les comorbiditats psiquiàtriques, l'habilitat cognitiva i els factors familiars, tant genètics com ambientals. Com a pas previ, es va fer un estudi de validació del codi diagnòstic d'FS que empren els registres suecs.

Les principals conclusions de la tesi es poden resumir en els enunciats següents:

I. El codi diagnòstic d'FS (F40.1) en el Registre nacional de pacients de Suècia és vàlid i fiable. La gravetat de símptomes i el grau de disfuncionalitat global dels pacients que tenen associat aquest codi és moderat.

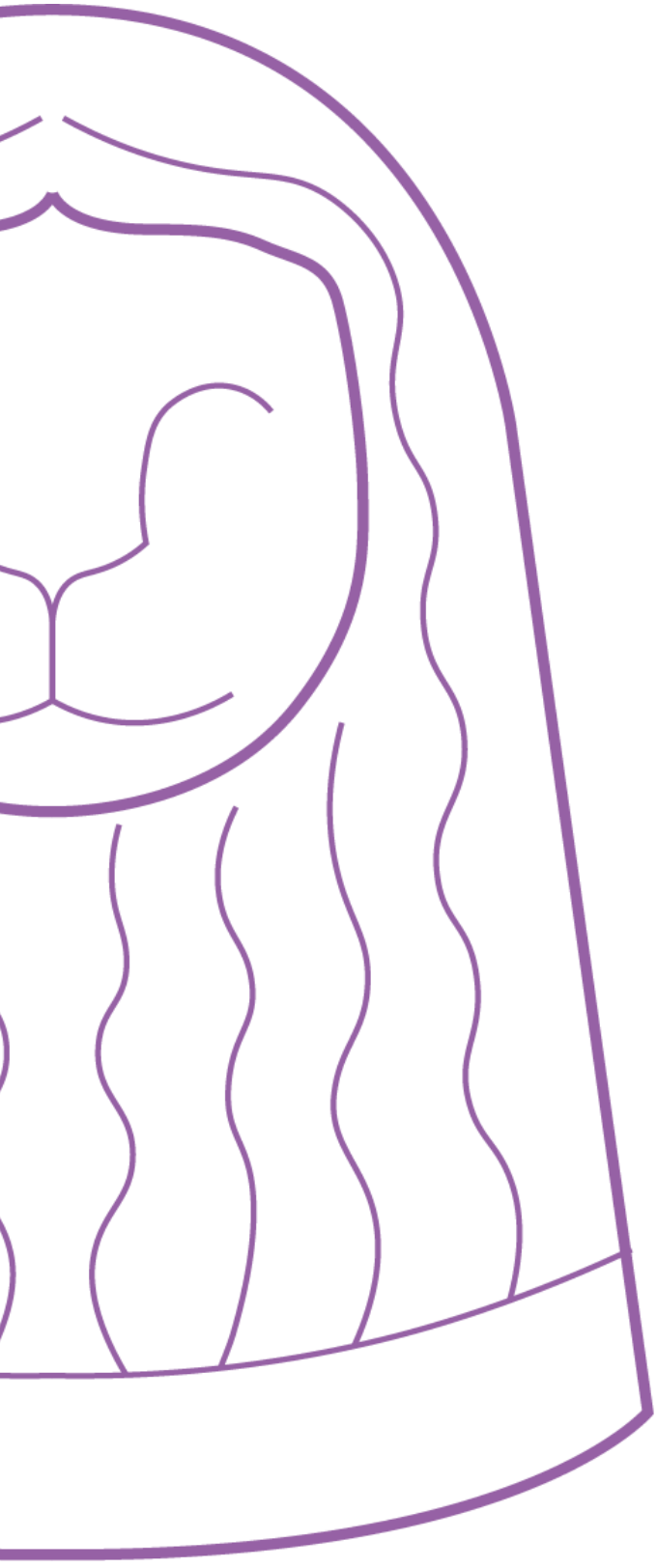
II. L'FS s'associa a un risc substancialment més gran de disminució del rendiment acadèmic en tots els nivells, des de l'educació obligatòria fins als estudis de postgrau, especialment en les dones. Aquesta associació no s'explica millor per la comorbiditat psiquiàtrica o pels factors familiars.

III. El TEPT s'associa a un risc substancialment més gran de disminució del rendiment acadèmic en tots els nivells, des de l'educació obligatòria fins als estudis universitaris. Aquesta associació no s'explica millor per la comorbiditat psiquiàtrica, la capacitat cognitiva general o els factors familiars.

IV. Examinar el rendiment acadèmic d'aquestes cohorts poblacionals amb persones amb FS o TEPT que busquen tractament contribueix a completar la nostra comprensió de l'impacte i el cost associat a aquests trastorns.

V. Aquest nou coneixement pot contribuir al desenvolupament d'iniciatives dels centres educatius, serveis socials, professionals de la salut mental i entitats polítiques per dissenyar, implementar i disseminar programes de prevenció i d'intervenció per a reduir la interferència funcional de les persones que conviuen amb un trastorn psiquiàtric.

7 REFERENCES



Aderka, I. M., Hofmann, S. G., Nickerson, A., Hermesh, H., Gilboa-Schechtman, E., & Marom, S. (2012). Functional impairment in social anxiety disorder. *Journal of Anxiety Disorders, 26*(3), 393-400. https://doi.org/10.1016/j.janxdis.2012.01.003

Afifi, T. O., Asmundson, G. J., Taylor, S., & Jang, K. L. (2010). The role of genes and environment on trauma exposure and posttraumatic stress disorder symptoms: a review of twin studies. *Clinical Psychology Review, 30*(1), 101-112. https://doi.org/10.1016/j.cpr.2009.10.002

Alonso, J., Angermeyer, M. C., Bernert, S., Bruffaerts, R., Brugha, T. S., Bryson, H., . . . EsemeD/Mhedea Investigators, E. S. o. t. E. o. M. D. P. (2004). Disability and quality of life impact of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta Psychiatrica Scandinavica* (420), 38-46. https://doi.org/10.1111/j.1600-0047.2004.00329.x

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders : DSM-IV-TR* (4. ed. / text revision. ed.). Washington, DC: Washington, DC: American Psychiatric Association.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders, Fifth Edition (DSM-5®)*: Washington, DC: American Psychiatric Association.

American Psychiatric Association. (2016). *Anxiety disorders : DSM-5 selections*: Arlington, VA : American Psychiatric Association Publishing.

Andrews, G., Slade, T., & Issakidis, C. (2002). Deconstructing current comorbidity: data from the Australian National Survey of Mental Health and Well-Being. *British Journal of Psychiatry, 181*(4), 306-314. https://doi.org/10.1192/bjp.181.4.306

Auerbach, R. P., Alonso, J., Axinn, W. G., Cuijpers, P., Ebert, D. D., Green, J. G., . . . Bruffaerts, R. (2016). Mental disorders among college students in the World Health Organization World Mental Health Surveys. *Psychological Medicine, 46*(14), 2955-2970. https://doi.org/10.1017/S0033291716001665

Auxemery, Y. (2012). Posttraumatic stress disorder (PTSD) as a consequence of the interaction between an individual genetic susceptibility, a traumatogenic event and a social context. *Encephale, 38*(5), 373-380. https://doi.org/10.1016/j.encep.2011.12.003

Bachrach, R., & Read, J. (2012). The Role of Posttraumatic Stress and Problem Alcohol Involvement in University Academic Performance. *Journal of Clinical Psychology, 68*. https://doi.org/ 10.1002/jclp.21874

Baptista, C. A., Loureiro, S. R., de Lima Osório, F., Zuardi, A. W., Magalhães, P. V., Kapczinski, F., . . . Crippa, J. A. S. (2012). Social phobia in Brazilian university students: Prevalence, under-recognition and academic impairment in women. *Journal of Affective Disorders, 136*(3), 857-861. https://doi.org/10.1016/j.jad.2011.09.022

Barlow, D. H. (2004). *Anxiety and its disorders: The nature and treatment of anxiety and panic*: Guilford press.

Beidel, D. C., Turner, S. M., & Morris, T. L. (2000). Behavioral Treatment of Childhood Social Phobia. *Journal of Consulting and Clinical Psychology, 68*(6), 1072-1080. https://doi.org/10.1037/0022-006X.68.6.1072

Belbasis, L., Köhler, C. A., Stefanis, N., Stubbs, B., van Os, J., Vieta, E., . . . Evangelou, E. (2018). Risk factors and peripheral biomarkers for schizophrenia spectrum disorders:

an umbrella review of meta-analyses. *Acta Psychiatrica Scandinavica, 137*(2), 88-97. https://doi.org/10.1111/acps.12847

Belfield, C., Levin, H. M. (2007). *The Price We Pay: Economic and Social Consequences of Inadequate Education*. Washington, DC: Brookings Institution Press.

Benjet, C., Bromet, E., Karam, E. G., Kessler, R. C., McLaughlin, K. A., Ruscio, A. M., . . . Koenen, K. C. (2016). The epidemiology of traumatic event exposure worldwide: results from the World Mental Health Survey Consortium. *Psychological Medicine, 46*(2), 327-343. https://doi.org/10.1017/s0033291715001981

Berger, R., & Gelkopf, M. (2009). School-based intervention for the treatment of tsunami-related distress in children: a quasi-randomized controlled trial. *Psychotherapy and Psychosomatics, 78*(6), 364-371. https://doi.org/10.1159/000235976.

Birkley, E. L., Eckhardt, C. I., & Dykstra, R. E. (2016). Posttraumatic Stress Disorder Symptoms, Intimate Partner Violence, and Relationship Functioning: A Meta-Analytic Review. *Journal of Traumatic Stress, 29*(5), 397-405. https://doi.org/10.1002/jts.22129

Blanco, C., Rubio, J., Wall, M., Wang, S., Jiu, C. J., & Kendler, K. S. (2014). Risk Factors For Anxiety Disorders: Common And Specific Effects In A National Sample. *Depression and Anxiety, 31*(9), 756-764. https://doi.org/10.1002/da.22247

Bonanno, G. A. (2004). Loss, Trauma, and Human Resilience: Have We Underestimated the Human Capacity to Thrive After Extremely Aversive Events? *American Psychologist, 59*(1), 20-28. https://doi.org/10.1037/0003-066X.59.1.20

Bortolato, B., Köhler, C. A., Evangelou, E., León-Caballero, J., Solmi, M., Stubbs, B., . . . Carvalho, A. F. (2017). Systematic assessment of environmental risk factors for bipolar disorder: an umbrella review of systematic reviews and meta-analyses. *Bipolar Disorders, 19*(2), 84-96. https://doi.org/10.1111/bdi.12490

Boyraz, G., Granda, R., Baker, C. N., Tidwell, L. L., & Waits, J. B. (2016). Posttraumatic stress, effort regulation, and academic outcomes among college students: A longitudinal study. *Journal of Consulting and Clinical Psychology, 63*(4), 475-486. https://doi.org/10.1037/cou0000102

Boyraz, G., Horne, S. G., Owens, A. C., & Armstrong, A. P. (2013). Academic achievement and college persistence of African American students with trauma exposure. *Journal of Consulting and Clinical Psychology, 60*(4), 582-592. https://doi.org/10.1037/a0033672

Braveman, P., & Gottlieb, L. (2014). The social determinants of health: it's time to consider the causes of the causes. *Public Health Reports, 129 Suppl 2*, 19-31. https://doi.org/10.1177/00333549141291S206

Brühl, A. B., Delsignore, A., Komossa, K., & Weidt, S. (2014). Neuroimaging in social anxiety disorder—A meta-analytic review resulting in a new neurofunctional model. *Neuroscience & Biobehavioral Reviews, 47*, 260-280. https://doi.org/10.1016/j.neubiorev.2014.08.003

Brunello, N., den Boer, J. A., Judd, L. L., Kasper, S., Kelsey, J. E., Lader, M., . . . Wittchen, H. U. (2000). Social phobia: diagnosis and epidemiology, neurobiology and pharmacology, comorbidity and treatment. *Journal of Affective Disorders, 60*(1), 61-74. https://doi.org/10.1016/S0165-0327(99)00140-8

Canton, J., Scott, K. M., & Glue, P. (2012). Optimal treatment of social phobia: systematic review and meta-analysis. *Neuropsychiatric Disease and Treatment, 8*, 203-215. https://doi.org/10.2147/ndt.S23317

Clarke, A. M., Bunting, B., & Barry, M. M. (2014). Evaluating the implementation of a school-based emotional well-being programme: a cluster randomized controlled trial of Zippy's Friends for children in disadvantaged primary schools. *Health Education Research, 29*(5), 786-798. https://doi.org/10.1093/her/cyu047

Clauss, J. A., & Blackford, J. U. (2012). Behavioral inhibition and risk for developing social anxiety disorder: a meta-analytic study. *Journal of the American Academy of Child & Adolescent Psychiatry, 51*(10), 1066-1075.e1061. https://doi.org/10.1016/j.jaac.2012.08.002

Cohen, A. K., & Syme, S. L. (2013). Education: A Missed Opportunity for Public Health Intervention. *American Journal of Public Health, 103*(6), 997-1001. https://doi.org/10.2105/AJPH.2012.300993

Craske, M. G., & Stein, M. B. (2016). Anxiety. *The Lancet, 388*(10063), 3048-3059. https://doi.org/10.1016/S0140-6736(16)30381-6

Dalman, C., Broms, J., Cullberg, J., & Allebeck, P. (2002). Young cases of schizophrenia identified in a national inpatient register. *Social Psychiatry and Psychiatric Epidemiology, 37*(11), 527-531. https://doi.org/10.1007/s00127-002-0582-3

Dalsgaard, S., McGrath, J., Østergaard, S. D., Wray, N. R., Pedersen, C. B., Mortensen, P. B., & Petersen, L. (2020). Association of Mental Disorder in Childhood and Adolescence With Subsequent Educational Achievement. *JAMA Psychiatry*. https://doi.org/10.1001/jamapsychiatry.2020.0217

Davidson, J. T., Foa, E. B., Huppert, J. D., Keefe, F. J., Franklin, M. E., Compton, J. S., . . . Gadde, K. M. (2004). Fluoxetine, comprehensive cognitive behavioral therapy, and placebo in generalized social phobia. *Archives of General Psychiatry, 61*(10), 1005-1013. https://doi.org/10.1001/archpsyc.61.10.1005

Davidson, J. T., Hughes, D. C., George, L. K., & Blazer, D. G. (1994a). The boundary of social phobia: Exploring the threshold. *Archives of General Psychiatry, 51*(12), 975-983. https://doi.org/10.1001/archpsyc.1994.03950120047008

de Girolamo, G., Dagani, J., Purcell, R., Cocchi, A., & McGorry, P. D. (2011). Age of onset of mental disorders and use of mental health services: needs, opportunities and obstacles. *Epidemiology and psychiatric sciences, 21*(1), 47-57. https://doi.org/10.1017/s2045796011000746

DiGangi, J. A., Gomez, D., Mendoza, L., Jason, L. A., Keys, C. B., & Koenen, K. C. (2013). Pretrauma risk factors for posttraumatic stress disorder: a systematic review of the literature. *Clinical Psychology Review, 33*(6), 728-744. https://doi.org/10.1016/j.cpr.2013.05.002

Druss, B. G., Hwang, I., Petukhova, M., Sampson, N. A., Wang, P. S., & Kessler, R. C. (2009). Impairment in role functioning in mental and chronic medical disorders in the United States: results from the National Comorbidity Survey Replication. *Molecular Psychiatry, 14*(7), 728-737. https://doi.org/10.1038/mp.2008.13

Durlak, J. A., Weissberg, R. P., Dymnicki, A. B., Taylor, R. D., & Schellinger, K. B. (2011). The Impact of Enhancing Students' Social and Emotional Learning: A Meta-Analysis

of School-Based Universal Interventions. *Child Development, 82*(1), 405-432. https://doi.org/10.1111/j.1467-8624.2010.01564.x

Ekbom, A. (2011). The Swedish Multi-generation Register. *Methods in Molecular Biology, 675*, 215-220. https://doi.org/10.1007/978-1-59745-423-0_10

Erwin, B. A., Heimberg, R. G., Marx, B. P., & Franklin, M. E. (2006). Traumatic and socially stressful life events among persons with social anxiety disorder. *Journal of Anxiety Disorders, 20*(7), 896-914. https://doi.org/10.1016/j.janxdis.2005.05.006

Esch, P., Bocquet, V., Pull, C., Couffignal, S., Lehnert, T., Graas, M., . . . Ansseau, M. (2014). The downward spiral of mental disorders and educational attainment: a systematic review on early school leaving. *BMC Psychiatry, 14*(1), 237. https://doi.org/10.1186/s12888-014-0237-4

Fang, F., Arnberg, F. K., Mataix-Cols, D., Fernández de la Cruz, L., Almqvist, C., Fall, K., . . . Song, H. (2019). Stress related disorders and risk of cardiovascular disease: population based, sibling controlled cohort study. *The BMJ, 365*. https://doi.org/10.1136/bmj.l1255

Federici, S., Bracalenti, M., Meloni, F., & Luciano, J. V. (2017). World Health Organization disability assessment schedule 2.0: An international systematic review. *Disability and Rehabilitation, 39*(23), 2347-2380. https://doi.org/10.1080/09638288.2016.1223177

Fehm, L., Pelissolo, A., Furmark, T., & Wittchen, H. U. (2005). Size and burden of social phobia in Europe. *European Neuropsychopharmacoly, 15*(4), 453-462. https://doi.org/10.1016/j.euroneuro.2005.04.002

Fox, A. S., & Kalin, N. H. (2014). A translational neuroscience approach to understanding the development of social anxiety disorder and its pathophysiology. *American Journal of Psychiatry, 171*(11), 1162-1173. https://doi.org/10.1176/appi.ajp.2014.14040449

Friedman, M. J., Resick, P. A., Bryant, R. A., Strain, J., Horowitz, M., & Spiegel, D. (2011). Classification of trauma and stressor-related disorders in DSM-5. *Depression and Anxiety, 28*(9), 737-749. https://doi.org/10.1002/da.20845

Fullana, M. A., Tortella-Feliu, M., Fernández de la Cruz, L., Chamorro, J., Pérez-Vigil, A., Ioannidis, J. P. A., . . . Radua, J. (2020). Risk and protective factors for anxiety and obsessive-compulsive disorders: an umbrella review of systematic reviews and meta-analyses. *Psychological Medicine, 50*(8), 1300-1315. https://doi.org/10.1017/s0033291719001247

Gabriel, P., & Liimatainen, M.-R. (2000). *Mental health in the workplace*. Geneva, Switzerland: International Labour Organization.

Gazelle, H., & Rubin, K. H. (2019). Social Withdrawal and Anxiety in Childhood and Adolescence: Interaction between Individual Tendencies and Interpersonal Learning Mechanisms in Development : Introduction to the Special Issue. *Journal of Abnormal Child Psychology, 47*(7), 1101-1106. https://doi.org/10.1007/s10802-019-00557-y

Gelernter, J., Sun, N., Polimanti, R., Pietrzak, R., Levey, D. F., Bryois, J., . . . Stein, M. B. (2019). Genome-wide association study of post-traumatic stress disorder reexperiencing symptoms in >165,000 US veterans. *Nature Neuroscience, 22*(9), 1394-1401. https://doi.org/10.1038/s41593-019-0447-7

Goodman, R. D., Miller, M. D., & West-Olatunji, C. A. (2012). Traumatic stress, socioeconomic status, and academic achievement among primary school students.

Psychological Trauma: Theory, Research, Practice, and Policy, *4*(3), 252-259. https://doi.org/10.1037/a0024912

Gradus, J. L. (2018). Posttraumatic Stress Disorder and Death From Suicide. *Current Psychiatry Reports*, *20*(11), 98. https://doi.org/10.1007/s11920-018-0965-0

Gradus, J. L., Antonsen, S., Svensson, E., Lash, T. L., Resick, P. A., & Hansen, J. G. (2015). Trauma, Comorbidity, and Mortality Following Diagnoses of Severe Stress and Adjustment Disorders: A Nationwide Cohort Study. *American Journal of Epidemiology*, *182*(5), 451-458. https://doi.org/10.1093/aje/kwv066

Gren-Landell, M., Tillfors, M., Furmark, T., Bohlin, G., Andersson, G., & Svedin, C. G. (2009). Social phobia in Swedish adolescents : prevalence and gender differences. *Social Psychiatry and Psychiatric Epidemiology*, *44*(1), 1-7. https://doi.org/10.1007/s00127-008-0400-7

Grubaugh, A. L., Zinzow, H. M., Paul, L., Egede, L. E., & Frueh, B. C. (2011). Trauma exposure and posttraumatic stress disorder in adults with severe mental illness: a critical review. *Clinical Psychology Review*, *31*(6), 883-899. https://doi.org/10.1016/j.cpr.2011.04.003

Guideline Development Panel for the Treatment of PTSD in Adults, A. P. A. (2019). Summary of the clinical practice guideline for the treatment of posttraumatic stress disorder (PTSD) in adults. *American Psychologist Journal*, *74*(5), 596-607. https://doi.org/10.1037/amp0000473

Gullone, E. (2000). The development of normal fear: A century of research. *Clinical Psychology Review*, *20*(4), 429-451. https://doi.org/10.1016/S0272-7358(99)00034-3

Hedman, E., Andersson, G., Ljótsson, B., Andersson, E., Rück, C., Mörtberg, E., & Lindefors, N. (2011). Internet-Based Cognitive Behavior Therapy vs. Cognitive Behavioral Group Therapy for Social Anxiety Disorder: A Randomized Controlled Non-inferiority Trial (Internet-Based CBT vs. Group CBT for SAD - A RCT). *PLoS One*, *6*(3), e18001. https://doi.org/10.1371/journal.pone.0018001

Helgesson, M., Tinghög, P., Niederkrotenthaler, T., Saboonchi, F., & Mittendorfer-Rutz, E. (2017). Labour-market marginalisation after mental disorders among young natives and immigrants living in Sweden. *BMC Public Health*, *17*(1), 593-512. https://doi.org/10.1186/s12889-017-4504-4

Hoff, R., Corbett, K., Mehlum, I. S., Mohn, F. A., Kristensen, P., Hanvold, T. N., & Gran, J. M. (2018). The impact of completing upper secondary education - a multi-state model for work, education and health in young men. *BMC Public Health*, *18*(1), 556-516. https://doi.org/10.1186/s12889-018-5420-y

Hofmann, S. G., & DiBartolo, P. M. (2014). *Social anxiety: clinical, developmental, and social perspectives* (3rd ed. ed.). London, England; Waltham, Massachusetts; San Diego, California: Academic Press.

Holen, S., Waaktaar, T., Lervåg, A., & Ystgaard, M. (2013). Implementing a Universal Stress Management Program for Young School Children: Are there Classroom Climate or Academic Effects? *Scandinavian Journal of Educational Research*, *57*(4), 420-444. https://doi.org/10.1080/00313831.2012.656320

Hollander, A.-C., Askegård, K., Iddon-Escalante, C., Holmes, E. A., Wicks, S., & Dalman, C. (2019). Validation study of randomly selected cases of PTSD diagnoses identified in a Swedish regional database compared with medical records: is the validity sufficient

for epidemiological research? *BMJ Open, 9*(12). https://doi.org/10.1136/bmjopen-2019-031964

Hoover, S. A., Sapere, H., Lang, J. M., Nadeem, E., Dean, K. L., & Vona, P. (2018). Statewide Implementation of an Evidence-Based Trauma Intervention in Schools. *School Psychology Quarterly, 33*(1), 44-53. https://doi.org/10.1037/spq0000248

Hugh-Jones, S., Beckett, S., Tumelty, E., & Mallikarjun, P. (2020). Indicated prevention interventions for anxiety in children and adolescents: a review and meta-analysis of school-based programs. *European Child & Adolescent Psychiatry*. https://doi.org/10.1007/s00787-020-01564-x

Idring, S., Rai, D., Dal, H., Dalman, C., Sturm, H., Zander, E., . . . Magnusson, C. (2012). Autism Spectrum Disorders in the Stockholm Youth Cohort: Design, Prevalence and Validity (Stockholm Youth Cohort Design). *PLoS One, 7*(7), e41280. https://doi.org/10.1371/journal.pone.0041280

Isomura, K., Boman, M., Ruck, C., Serlachius, E., Larsson, H., Lichtenstein, P., & Mataix-Cols, D. (2015). Population-based, multi-generational family clustering study of social anxiety disorder and avoidant personality disorder. *Psychological Medicine, 45*(8), 1581-1589. https://doi.org/10.1017/s0033291714002116

Jakobsson, G. L., Sternegård, E., Olén, O., Myrelid, P., Ljung, R., Strid, H., . . . Ludvigsson, J. F. (2017). Validating inflammatory bowel disease (IBD) in the Swedish National Patient Register and the Swedish Quality Register for IBD (SWIBREG). *Scandinavian Journal of Gastroenterology, 52*(2), 216-221. https://doi.org/10.1080/00365521.2016.1246605

James, S. L., Abate, D., Abate, K. H., Abay, S. M., Abbafati, C., Abbasi, N., . . . Murray, C. J. L. (2018). Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet, 392*(10159), 1789-1858. https://doi.org/10.1016/S0140-6736(18)32279-7

Jaycox, L. H., Kataoka, S. H., Stein, B. D., Langley, A. K., & Wong, M. (2012). Cognitive Behavioral Intervention for Trauma in Schools. *Journal of Applied School Psychology, 28*(3), 239-255. https://doi.org/10.1080/15377903.2012.695766

Jordan, C. E., Combs, J. L., & Smith, G. T. (2014). An Exploration of Sexual Victimization and Academic Performance Among College Women. *Trauma Violence Abuse, 15*(3), 191-200. https://doi.org/10.1177/1524838014520637

Kagan, J., Reznick, J. S., Clarke, C., Snidman, N., & Garcia-Coll, C. (1984). Behavioral inhibition to the unfamiliar. *Child Development, 55*(6), 2212-2225. https://doi.org/10.2307/1129793

Kalra, H., Kamath, P., Trivedi, J. K., & Janca, A. (2008). Caregiver burden in anxiety disorders. *Current Opinion in Psychiatry, 21*(1), 70-73. https://doi.org/10.1097/YCO.0b013e3282f2dfca

Katzelnick, D. J., & Greist, J. H. (2001). Social anxiety disorder: an unrecognized problem in primary care. *Journal of Clinical Psychiatry, 62 Suppl 1*, 11-15; discussion 15-16.

Katzman, M. A., Bleau, P., Blier, P., Chokka, P., Kjernisted, K., Van Ameringen, M., . . . Walker, J. R. (2014). Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. *BMC Psychiatry, 14 Suppl 1*, S1. https://doi.org/10.1186/1471-244x-14-s1-s1

Kessler, R. C. (2003). The impairments caused by social phobia in the general population: implications for intervention. *Acta Psychiatrica Scandinavica, 108*(s417), 19-27. https://doi.org/10.1034/j.1600-0447.108.s417.2.x

Kessler, R. C., Aguilar-Gaxiola, S., Alonso, J., Benjet, C., Bromet, E. J., Cardoso, G., . . . Koenen, K. C. (2017). Trauma and PTSD in the WHO World Mental Health Surveys. *European Journal of Psychotraumatology, 8*(sup5), 1353383. https://doi.org/10.1080/20008198.2017.1353383

Kessler, R. C., Amminger, G. P., Aguilar-Gaxiola, S., Alonso, J., Lee, S., & Ustun, T. B. (2007). Age of onset of mental disorders: a review of recent literature. *Current Opinion in Psychiatry, 20*(4), 359-364. https://doi.org/10.1097/YCO.0b013e32816ebc8c

Kessler, R. C., Angermeyer, M., Anthony, J. C., R, D. E. G., Demyttenaere, K., Gasquet, I., . . . Ustün, T. B. (2007). Lifetime prevalence and age-of-onset distributions of mental disorders in the World Health Organization's World Mental Health Survey Initiative. *World Psychiatry, 6*(3), 168-176.

Koenen, K. C., Ratanatharathorn, A., Ng, L., McLaughlin, K. A., Bromet, E. J., Stein, D. J., Kessler, R. C. (2017). Posttraumatic stress disorder in the World Mental Health Surveys. *Psychological Medicine, 47*(13), 2260-2274. https://doi.org/10.1017/S0033291717000708

Köhler, C. A., Evangelou, E., Stubbs, B., Solmi, M., Veronese, N., Belbasis, L., . . . Carvalho, A. F. (2018). Mapping risk factors for depression across the lifespan: An umbrella review of evidence from meta-analyses and Mendelian randomization studies. *Journal of Psychiatric Research, 103*, 189-207. https://doi.org/10.1016/j.jpsychires.2018.05.020

Kremen, W. S., Koenen, K. C., Afari, N., & Lyons, M. J. (2012). Twin studies of posttraumatic stress disorder: differentiating vulnerability factors from sequelae. *Neuropharmacology, 62*(2), 647-653. https://doi.org/10.1016/j.neuropharm.2011.03.012

Kremen, W. S., Koenen, K. C., Boake, C., Purcell, S., Eisen, S. A., Franz, C. E., . . . Lyons, M. J. (2007). Pretrauma cognitive ability and risk for posttraumatic stress disorder: a twin study. *Archives of General Psychiatry, 64*(3), 361-368. https://doi.org/10.1001/archpsyc.64.3.361

Lebois, L. A. M., Wolff, J. D., & Ressler, K. J. (2016). Neuroimaging genetic approaches to Posttraumatic Stress Disorder. *Experimental Neurology, 284*, 141-152. https://doi.org/10.1016/j.expneurol.2016.04.019

Leichsenring, F., & Leweke, F. (2017). Social Anxiety Disorder. *The New England Journal of Medicine, 376*(23), 2255-2264. https://doi.org/10.1056/NEJMcp1614701

Lereya, S. T., Patel, M., dos Santos, J. P. G. A., & Deighton, J. (2019). Mental health difficulties, attainment and attendance: a cross-sectional study. *European Child & Adolescent Psychiatry, 28*(8), 1147-1152. https://doi.org/10.1007/s00787-018-01273-6

Lijster, J. M., Dieleman, G. C., Utens, E., Dierckx, B., Wierenga, M., Verhulst, F. C., & Legerstee, J. S. (2018). Social and academic functioning in adolescents with anxiety disorders: A systematic review. *Journal of Affective Disorders, 230*, 108-117. https://doi.org/10.1016/j.jad.2018.01.008

Lijster, J. M., Dierckx, B., Utens, E. M., Verhulst, F. C., Zieldorff, C., Dieleman, G. C., & Legerstee, J. S. (2017). The Age of Onset of Anxiety Disorders. *The Canadian Journal of Psychiatry, 62*(4), 237-246. https://doi.org/10.1177/0706743716640757

Lochner, L. (2004). Education, Work, And Crime: A Human Capital Approach. *International Economic Review, 45*(3), 811-843. https://doi.org/10.1111/j.0020-6598.2004.00288.x

Ludvigsson, J. F., Almqvist, C., Bonamy, A. E., Ljung, R., Michaëlsson, K., Neovius, M., . . . Ye, W. (2016). Registers of the Swedish total population and their use in medical research. *European Journal of Epidemiology, 31*(2), 125-136. https://doi.org/10.1007/s10654-016-0117-y

Ludvigsson, J. F., Andersson, E., Ekbom, A., Feychting, M., Kim, J. L., Reuterwall, C., . . . Olausson, P. O. (2011). External review and validation of the Swedish national inpatient register. *BMC Public Health, 11*, 450. https://doi.org/10.1186/1471-2458-11-450

Ludvigsson, J. F., Otterblad-Olausson, P., Pettersson, B. U., & Ekbom, A. (2009). The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *European Journal of Epidemiology, 24*(11), 659-667. https://doi.org/10.1007/s10654-009-9350-y

Ludvigsson, J. F., Svedberg, P., Olén, O., Bruze, G., & Neovius, M. (2019). The longitudinal integrated database for health insurance and labour market studies (LISA) and its use in medical research. *European Journal of Epidemiology, 34*, 423-437. https://doi.org/10.1007/s10654-019-00511-8

Lynn, R., & Mikk, J. (2009). National IQs predict educational attainment in math, reading and science across 56 nations. *Intelligence, 37*(3), 305-310. https://doi.org/10.1016/j.intell.2009.01.002

Marks, I. M., & Gelder, M. G. (1965). A controlled retrospective study of behaviour therapy in phobic patients. *The British Journal of Psychiatry, 111*, 561-573. https://doi.org/10.1192/bjp.111.476.561

Masia Warner, C., Colognori, D., Brice, C., Herzig, K., Mufson, L., Lynch, C., . . . Klein, R. G. (2016). Can school counselors deliver cognitive-behavioral treatment for social anxiety effectively? A randomized controlled trial. *Journal of Child Psychology and Psychiatry, 57*(11), 1229-1238. https://doi.org/10.1111/jcpp.12550

Masia Warner, C., Colognori, D., & Lynch, C. (2018). *Helping Students Overcome Social Anxiety Skills for Academic and Social Success (SASS)*. New York: Guilford Press.

Masia Warner, C., Fisher, P. H., Shrout, P. E., Rathor, S., & Klein, R. G. (2007). Treating adolescents with social anxiety disorder in school: an attention control trial. *Journal of Child Psychology and Psychiatry, 48*(7), 676-686. https://doi.org/10.1111/j.1469-7610.2007.01737.x

Masia Warner, C., Klein, R. G., Dent, H. C., Fisher, P. H., Alvir, J., Albano, A. M., & Guardino, M. (2005). School-based intervention for adolescents with social anxiety disorder: results of a controlled study. *Journal Abnormal Child Psychology, 33*(6), 707-722. https://doi.org/10.1007/s10802-005-7649-z

Mayo-Wilson, E., Dias, S., Mavranezouli, I., Kew, K., Clark, D. M., Ades, A. E., & Pilling, S. (2014). Psychological and pharmacological interventions for social anxiety disorder in adults: a systematic review and network meta-analysis. *Lancet Psychiatry, 1*(5), 368-376. https://doi.org/10.1016/s2215-0366(14)70329-3

McDaid, D., Hewlett, E., & Park, A.-L. (2017). Understanding effective approaches to promoting mental health and preventing mental illness. *OECD Health Working Papers*, No. 97. Paris: OECD Publishing. https://doi.org/10.1787/bc364fb2-en

Mendelson, T., Tandon, S. D., O'Brennan, L., Leaf, P. J., & Ialongo, N. S. (2015). Brief report: Moving prevention into schools: The impact of a trauma-informed school-based intervention. *Journal of Adolescence, 43*, 142-114. https://doi.org/10.1016/j.adolescence.2015.05.017

Mojtabai, R., Stuart, E. A., Hwang, I., Eaton, W. W., Sampson, N., & Kessler, R. C. (2015). Long-term effects of mental disorders on educational attainment in the National Comorbidity Survey ten-year follow-up. *Social Psychiatry and Psychiatric Epidemiology, 50*(10), 1577-1591. https://doi.org/10.1007/s00127-015-1083-5

Morissette, S. B., Ryan-Gonzalez, C., Yufik, T., DeBeer, B. B., Kimbrel, N. A., Sorrells, A. M., . . . Meyer, E. C. (2019). The effects of posttraumatic stress disorder symptoms on educational functioning in student veterans. *Psychological Services*. https://doi.org/10.1037/ser0000356 Advance online publication

Murray, C. J., Richards, M. A., Newton, J. N., Fenton, K. A., Anderson, H. R., Atkinson, C., . . . Davis, A. (2013). UK health performance: findings of the Global Burden of Disease Study 2010. *Lancet, 381*(9871), 997-1020. https://doi.org/10.1016/S0140-6736(13)60355-4

National Guidance Alliance. (2013). *Social Anxiety Disorder: Recognition, Assessment and Treatment.* Leicester (UK): British Psychological Society & The Royal College of Psychiatrists.

National Guideline Alliance. (2018). *Post-traumatic stress disorder.* (Vol. No. 116). London (UK): National Institute for Health and Care Excellence.

Niederkrotenthaler, T., Tinghög, P., Goldman-Mellor, S., Wilcox, H. C., Gould, M., & Mittendorfer-Rutz, E. (2016). Medical and Social Determinants of Subsequent Labour Market Marginalization in Young Hospitalized Suicide Attempters. *PLoS One, 11*(1), e0146130. https://doi.org/10.1371/journal.pone.0146130

Nievergelt, C. M., Maihofer, A. X., Klengel, T., Atkinson, E. G., Chen, C. Y., Choi, K. W., . . . Koenen, K. C. (2019). International meta-analysis of PTSD genome-wide association studies identifies sex- and ancestry-specific genetic risk loci. *Nature Communications, 10*(1), 4558. https://doi.org/10.1038/s41467-019-12576-w

Nissen, L. R., Karstoft, K. I., Vedtofte, M. S., Nielsen, A. B. S., Osler, M., Mortensen, E. L., . . . Andersen, S. B. (2017). Cognitive ability and risk of post-traumatic stress disorder after military deployment: an observational cohort study. *BJPsych Open, 3*(6), 274-280. https://doi.org/10.1192/bjpo.bp.117.005736

Nordh, M., Vigerland, S., Öst, L.-G., Ljótsson, B., Mataix-Cols, D., Serlachius, E., & Högström, J. (2017). Therapist-guided internet-delivered cognitive–behavioural therapy supplemented with group exposure sessions for adolescents with social anxiety disorder: a feasibility trial. *BMJ Open, 7*(12). https://doi.org/10.1136/bmjopen-2017-018345

Norton, A. R., & Abbott, M. J. (2017). The Role of Environmental Factors in the Aetiology of Social Anxiety Disorder: A Review of the Theoretical and Empirical Literature. *Behaviour Change, 34*(2), 76-97. https://doi.org/10.1017/bec.2017.7

OECD. (2001). *The Well-being of Nations: the role of human and social capital*. Paris: OECD Publishing. https://doi.org/10.1787/9789264189515-en.

OECD. (2012). *Equity and Quality in Education*. Paris: OECD Publishing. https://doi.org/10.1787/9789264130852-en.

OECD . (2018). *Health at a Glance: Europe 2018*: *State of Health in the EU Cycle*. Paris: OECD Publishing. https://doi.org/10.1787/health_glance_eur-2018-en.

OECD. (2019a). *Education at a Glance 2019*. Paris: OECD Publishing. https://doi.org/10.1787/f8d7880d-en.

OECD. (2019b). *PISA 2018 Assessment and Analytical Framework*. Paris: OECD Publishing. https://doi.org/10.1787/b25efab8-en.

Ohayon, M. M., & Schatzberg, A. F. (2010). Social phobia and depression: prevalence and comorbidity. *Journal of Psychosomatic Research, 68*(3), 235-243. https://doi.org/10.1016/j.jpsychores.2009.07.018

Olatunji, B. O., Cisler, J. M., & Tolin, D. F. (2007). Quality of life in the anxiety disorders: A meta-analytic review. *Clinical Psychology Review, 27*(5), 572-581. https://doi.org/10.1016/j.cpr.2007.01.015

Patalay, P., Gondek, D., Moltrecht, B., Giese, L., Curtin, C., Stanković, M., & Savka, N. (2017). Mental health provision in schools: approaches and interventions in 10 European countries. *Global Mental Health, 4*, e10. https://doi.org/10.1017/gmh.2017.6

Paulus, F. W., Ohmann, S., & Popow, C. (2016). Practitioner Review: School-based interventions in child mental health. *Journal of Child Psychology and Psychiatry, 57*(12), 1337-1359. https://doi.org/10.1111/jcpp.12584

Pekkarinen, T. (2012). Gender differences in education. *Nordic Economic Policy Review Conference*, 1, 165-197

Pereira, J. L., Guedes-Carneiro, G. M., Netto, L. R., Cavalcanti-Ribeiro, P., Lira, S., Nogueira, J. F., . . . Quarantini, L. C. (2018). Types of Trauma, Posttraumatic Stress Disorder, and Academic Performance in a Population of University Students. *Journal of Nervous and Mental Disease, 206*(7), 507-512. https://doi.org/10.1097/nmd.0000000000000842

Pérez-Vigil, A., Fernández de la Cruz, L., Brander, G., Isomura, K., Jangmo, A., Feldman, I., . . . Mataix-Cols, D. (2018). Association of Obsessive-Compulsive Disorder With Objective Indicators of Educational Attainment A Nationwide Register-Based Sibling Control Study. *JAMA Psychiatry, 75*(1), 47-55. https://doi.org/10.1001/jamapsychiatry.2017.3523

Pérez-Vigil, A., Fernández de la Cruz, L., Brander, G., Isomura, K., Jangmo, A., Kuja-Halkola, R., . . . Mataix-Cols, D. (2018). Association of Tourette Syndrome and Chronic Tic Disorders With Objective Indicators of Educational Attainment: A Population-Based Sibling Comparison Study. *JAMA Neurology, 75*(9), 1098-1105. https://doi.org/10.1001/jamaneurol.2018.1194

Pérez-Vigil, A., Mittendorfer-Rutz, E., Helgesson, M., Fernández de la Cruz, L., & Mataix-Cols, D. (2019). Labour market marginalisation in obsessive–compulsive disorder: a nationwide register-based sibling control study. *Psychological Medicine, 49*(6), 1015-1024. https://doi.org/10.1017/S0033291718001691

Pietrzak, R. H., Goldstein, R. B., Southwick, S. M., & Grant, B. F. (2011). Prevalence and Axis I comorbidity of full and partial posttraumatic stress disorder in the United States: Results from Wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions. *Journal of Anxiety Disorders, 25*(3), 456-465. https://doi.org/10.1016/j.janxdis.2010.11.010

Pilling, S., Mayo-Wilson, E., Mavranezouli, I., Kew, K., Taylor, C., Clark, D. M., & Guideline Development, G. (2013). Recognition, assessment and treatment of social anxiety disorder: summary of NICE guidance. *BMJ, 346*, f2541. https://doi.org/10.1136/bmj.f2541

Pitman, R. K., Rasmusson, A. M., Koenen, K. C., Shin, L. M., Orr, S. P., Gilbertson, M. W., . . . Liberzon, I. (2012). Biological studies of post-traumatic stress disorder. *Nature Reviews Neuroscience, 13*(11), 769-787. https://doi.org/10.1038/nrn3339

Polimanti, R., Ratanatharathorn, A., Maihofer, A. X., Choi, K. W., Stein, M. B., Morey, R. A., . . . Gelernter, J. (2019). Association of Economic Status and Educational Attainment With Posttraumatic Stress Disorder: A Mendelian Randomization Study. *JAMA Network Open, 2*(5), e193447. https://doi.org/10.1001/jamanetworkopen.2019.3447

Porche, M. V., Costello, D. M., & Rosen-Reynoso, M. (2016). Adverse Family Experiences, Child Mental Health, and Educational Outcomes for a National Sample of Students. *School Mental Health, 8*(1), 44-60. https://doi.org/10.1007/s12310-016-9174-3

Porche, M. V., Fortuna, L. R., Lin, J., & Alegria, M. (2011). Childhood Trauma and Psychiatric Disorders as Correlates of School Dropout in a National Sample of Young Adults. *Child Development, 82*(3), 982-998. https://doi.org/10.1111/j.1467-8624.2010.01534.x

Radua, J., Ramella-Cravaro, V., Ioannidis, J. P. A., Reichenberg, A., Phiphopthatsanee, N., Amir, T., . . . Fusar-Poli, P. (2018). What causes psychosis? An umbrella review of risk and protective factors. *World Psychiatry, 17*(1), 49-66. https://doi.org/10.1002/wps.20490

Ranta, K., La Greca, A. M., Kaltiala-Heino, R., & Marttunen, M. (2016). Social Phobia and Educational and Interpersonal Impairments in Adolescence: A Prospective Study. *Child Psychiatry & Human Development, 47*(4), 665-677. https://doi.org/10.1007/s10578-015-0600-9

Resick, P. A., & Miller, M. W. (2009). Posttraumatic stress disorder: Anxiety or traumatic stress disorder? *Journal of Traumatic Stress, 22*(5), 384-390. https://doi.org/10.1002/jts.20437

Reynolds, A. J., Ou, S. R., & Temple, J. A. (2018). A Multicomponent, Preschool to Third Grade Preventive Intervention and Educational Attainment at 35 Years of Age. *JAMA Pediatrics, 172*(3), 247-256. https://doi.org/10.1001/jamapediatrics.2017.4673

Rimfeld, K., Malanchini, M., Krapohl, E., Hannigan, L. J., Dale, P. S., & Plomin, R. (2018). The stability of educational achievement across school years is largely explained by genetic factors. *NPJ Science of Learning, 3*(1). https://doi.org/10.1038/s41539-018-0030-0

Rolfsnes, E. S., & Idsoe, T. (2011). School-based intervention programs for PTSD symptoms: a review and meta-analysis. *Journal of Traumatic Stress, 24*(2), 155. https://doi.org/10.1002/jts.20622

Rosén, M. (2002). National Health Data Registers: a Nordic heritage to public health. *Scandinavian Journal of Public Health, 30*(2), 81-85. https://doi.org/10.1017/bec.2017.7

Rossen, E. A., & Hull, R. (2013). *Supporting and educating traumatized students: a guide for school-based professionals*. Oxford: Oxford University Press.

Rück, C., Larsson, K. J., Lind, K., Perez-Vigil, A., Isomura, K., Sariaslan, A., . . . Mataix-Cols, D. (2015). Validity and reliability of chronic tic disorder and obsessive-compulsive disorder diagnoses in the Swedish National Patient Register. *BMJ Open, 5*(6), e007520. https://doi.org/10.1136/bmjopen-2014-007520

Ruscio, A. M., Brown, T. A., Chiu, W. T., Sareen, J., Stein, M. B., & Kessler, R. C. (2008). Social fears and social phobia in the USA: results from the National Comorbidity Survey Replication. *Psychological Medicine, 38*(1), 15-28. https://doi.org/10.1017/s0033291707001699

Salzer, S., Stefini, A., Kronmüller, K. T., Leibing, E., Leichsenring, F., Henningsen, P., . . . Steil, R. (2018). Cognitive-Behavioral and Psychodynamic Therapy in Adolescents with Social Anxiety Disorder: A Multicenter Randomized Controlled Trial. *Psychotherapy and Psychosomatics, 87*(4), 223-233. https://doi.org/10.1159/000488990

Scaini, S., Belotti, R., & Ogliari, A. (2014). Genetic and environmental contributions to social anxiety across different ages: a meta-analytic approach to twin data. *Journal of Anxiety Disorders, 28*(7), 650-656. https://doi.org/10.1016/j.janxdis.2014.07.002

Scaini, S., Belotti, R., Ogliari, A., & Battaglia, M. (2016). A comprehensive meta-analysis of cognitive-behavioral interventions for social anxiety disorder in children and adolescents. *Journal of Anxiety Disorders, 42*, 105-112. https://doi.org/10.1016/j.janxdis.2016.05.008

Schlechter, M., & Milevsky, A. (2010). Parental level of education: associations with psychological well-being, academic achievement and reasons for pursuing higher education in adolescence. *Educational Psychology, 30*(1), 1-10. https://doi.org/10.1080/01443410903326084

Scott, J. C., Matt, G. E., Wrocklage, K. M., Crnich, C., Jordan, J., Southwick, S. M., . . . Schweinsburg, B. C. (2015). A quantitative meta-analysis of neurocognitive functioning in posttraumatic stress disorder. *Psychological Bulletin, 141*(1), 105-140. https://doi.org/10.1037/a0038039

Sellers, R., Maughan, B., Pickles, A., Thapar, A., & Collishaw, S. (2015). Trends in parent- and teacher-rated emotional, conduct and ADHD problems and their impact in prepubertal children in Great Britain: 1999–2008. *Journal of Child Psychology and Psychiatry, 56*(1), 49-57. https://doi.org/10.1111/jcpp.12273

Sellgren, C., Landen, M., Lichtenstein, P., Hultman, C. M., & Langstrom, N. (2011). Validity of bipolar disorder hospital discharge diagnoses: file review and multiple register linkage in Sweden. *Acta Psychiatrica Scandinavica, 124*(6), 447-453. https://doi.org/10.1111/j.1600-0447.2011.01747.x

Shakeshaft, N. G., Trzaskowski, M., McMillan, A., Rimfeld, K., Krapohl, E., Haworth, C. M. A., . . . Plomin, R. (2013). Strong Genetic Influence on a UK Nationwide Test of Educational Achievement at the End of Compulsory Education at Age 16. *PLoS One, 8*(12), e80341. https://doi.org/10.1371/journal.pone.0080341

Shalev, A., Gevonden, M., Ratanatharathorn, A., Laska, E., van Der Mei, W. F., Qi, W., . . . Koenen, K. C. (2019). Estimating the risk of PTSD in recent trauma survivors: results of the International Consortium to Predict PTSD (ICPP). *World Psychiatry, 18*(1), 77. https://doi.org/10.1002/wps.20608

Shalev, A., Liberzon, I., & Marmar, C. (2017). Post-Traumatic Stress Disorder. *New England Journal of Medicine, 376*(25), 2459-2469. https://doi.org/10.1056/NEJMra1612499

Shavit, Y., & Muller, W. (1998). *From School to Work. A Comparative Study of Educational Qualifications and Occupational Destinations*. Oxford: Claredon press.

Sofia, L., Elke, T., Åke, S., Katarina Steen, C., Martin, E., & Ingemar, F. P. (2014). Validity of diagnostic codes and prevalence of physician-diagnosed psoriasis and psoriatic arthritis in southern Sweden--a population-based register study. *PLoS One, 9*(5), e98024. https://doi.org/10.1371/journal.pone.0098024

Song, H., Fall, K., Fang, F., Erlendsdóttir, H., Lu, D., Mataix-Cols, D., . . . Valdimarsdóttir, U. A. (2019). Stress related disorders and subsequent risk of life threatening infections: population based sibling controlled cohort study. *The BMJ, 367*. https://doi.org/10.1136/bmj.l5784

Spence, S. H., & Rapee, R. M. (2016). The etiology of social anxiety disorder: An evidence-based model. *Behaviour Research and Therapy, 86*, 50-67. https://doi.org/10.1016/j.brat.2016.06.007

Statistics Sweden. (2013). Cause of death. Retrieved from http://www.socialstyrelsen.se/statistics/statisticaldatabase/help/causeofdeath

Stein, B. D., Lim, C. C. W., Roest, A. M., de Jonge, P., Aguilar-Gaxiola, S., Al-Hamzawi, A., . . . Scott, K. M. (2017). The cross-national epidemiology of social anxiety disorder: Data from the World Mental Health Survey Initiative. *BMC Medicine, 15*(1), 143. https://doi.org/10.1186/s12916-017-0889-2

Stein, M. B., & Andrews, A. M. (2015). Serotonin States and Social Anxiety. *JAMA Psychiatry, 72*(8), 845-847. https://doi.org/10.1001/jamapsychiatry.2015.0486

Stein, M. B., Chen, C. Y., Jain, S., Jensen, K. P., He, F., Heeringa, S. G., . . . Gelernter, J. (2017). Genetic risk variants for social anxiety. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 174*(2), 120-131. https://doi.org/10.1002/ajmg.b.32520

Stein, M. B., & Kean, Y. M. (2000). Disability and quality of life in social phobia: epidemiologic findings. *American Journal of Psychiatry, 157*(10), 1606-1613. https://doi.org/10.1176/appi.ajp.157.10.1606

Steinert, C., Hofmann, M., Leichsenring, F., & Kruse, J. (2013). What do we know today about the prospective long-term course of social anxiety disorder? A systematic literature review. *Journal of Anxiety Disorders, 27*(7), 692-702. https://doi.org/10.1016/j.janxdis.2013.08.002

Storch, E. A., & Crisp, H. L. (2004). Introduction: Taking It to the Schools—Transporting Empirically Supported Treatments for Childhood Psychopathology to the School Setting. *Clinical Child and Family Psychology Review, 7*(4), 191-193. https://doi.org/10.1007/s10567-004-6084-y

Substance Abuse and Mental Health Services Administration. (2014). *SAMHSA's Concept of Trauma and Guidance for a Trauma-Informed Approach*. NHS Publication No. 14-4884. Rockville, MD: Substance Abuse and Mental Health Services Administration.

Sweeney, C., Warner, C. M., Brice, C., Stewart, C., Ryan, J., Loeb, K. L., & McGrath, R. E. (2015). Identification of Social Anxiety in Schools: The Utility of a Two-Step Screening Process. *Contemporary School Psychology, 19*(4), 268-275. https://doi.org/10.1007/s40688-015-0055-9

Sylvers, P., Lilienfeld, S. O., & LaPrairie, J. L. (2011). Differences between trait fear and trait anxiety: Implications for psychopathology. *Clinical Psychology Review, 31*(1), 122-137. https://doi.org/10.1016/j.cpr.2010.08.004

The Swedish National Agency for Education. (2018). National School Register. Retrieved from https://www.skolverket.se/.

Tortella-Feliu, M., Fullana, M. A., Pérez-Vigil, A., Torres, X., Chamorro, J., Littarelli, S. A., . . . Fernández de la Cruz, L. (2019). Risk factors for posttraumatic stress disorder: An umbrella review of systematic reviews and meta-analyses. *Neuroscience & Biobehavioral Reviews, 107*, 154-165. https://doi.org/10.1016/j.neubiorev.2019.09.013

Ustün, B. T., Chatterji, S., Kostanjsek, N., Rehm, J., Kennedy, C., Epping-Jordan, J., . . . Pull, C. (2010). Developing the World Health Organization Disability Assessment Schedule 2.0. *Bull World Health Organization, 88*(11), 815-823. https://doi.org/10.2471/blt.09.067231

Ustün, B. T., & Kennedy, C. (2009). What is "functional impairment"? Disentangling disability from clinical significance. *World Psychiatry, 8*(2), 82-85. https://doi.org/10.1002/j.2051-5545.2009.tb00219.x

Van Ameringen, M., Mancini, C., & Farvolden, P. (2003). The impact of anxiety disorders on educational achievement. *Journal of Anxiety Disorders, 17*(5), 561-571. https://doi.org/10.1016/S0887-6185(02)00228-1

Van der Kolk, B. A., Roth, S., Pelcovitz, D., Sunday, S., & Spinazzola, J. (2005). Disorders of extreme stress: The empirical foundation of a complex adaptation to trauma. *Journal of Traumatic Stress: Official Publication of the International Society for Traumatic Stress Studies, 18*(5), 389-399. https://doi.org/10.1002/jts.20047.

Van Hek, M., Kraaykamp, G., & Wolbers, M. H. J. (2016). Comparing the gender gap in educational attainment: the impact of emancipatory contexts in 33 cohorts across 33 countries. *Educational Research and Evaluation, 22*(5-6), 260-282. https://doi.org/10.1080/13803611.2016.1256222

Vona, P., Wilmoth, P., Jaycox, L., McMillen, J., Kataoka, S., Wong, M., . . . Stein, B. (2014). A Web-Based Platform to Support an Evidence-Based Mental Health Intervention: Lessons From the CBITS Web Site. *Psychiatric Services, 65*(11), 1381-1384. https://doi.org/10.1176/appi.ps.201300512

Voyer, D., & Voyer, S. D. (2014). Gender differences in scholastic achievement: a meta-analysis. *Psychological Bulletin, 140*(4), 1174-1204. https://doi.org/10.1037/a0036620

Wald, J., & Taylor, S. (2009). Work Impairment and Disability in Posttraumatic Stress Disorder: A Review and Recommendations for Psychological Injury Research and Practice. *Psychological Injury and Law, 2*(3), 254-262. https://doi.org/10.1007/s12207-009-9059-y

Weare, K., & Nind, M. (2011). Mental health promotion and problem prevention in schools: what does the evidence say? *Health Promotion International, 26*(suppl_1), i29-i69. https://doi.org/10.1093/heapro/dar075

Whiteford, H. A., Degenhardt, L., Rehm, J., Baxter, A. J., Ferrari, A. J., Erskine, H. E., . . . Vos, T. (2013). Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. *The Lancet, 382*(9904), 1575-1586. https://doi.org/10.1016/S0140-6736(13)61611-6

Wickersham, A., Dickson, H., Jones, R., Pritchard, M., Stewart, R., Ford, T., & Downs, J. (2020). Educational attainment trajectories among children and adolescents with depression, and the role of sociodemographic characteristics: longitudinal data-linkage study. *The British Journal of Psychiatry*, 1-7. https://doi.org/10.1192/bjp.2020.160

Williams, R. L. (2000). A note on robust variance estimation for cluster-correlated data. *Biometrics, 56*(2), 645-646. https://doi.org/10.1111/j.0006-341x.2000.00645.x

Winters, N. C., Collett, B. R., & Myers, K. M. (2005). Ten-year review of rating scales, VII: scales assessing functional impairment. *Journal of the American Academy of Child & Adolescent Psychiatry, 44*(4), 309-338; discussion 339-342. https://doi.org/10.1097/01.chi.0000153230.57344.cd

Wittchen, H. U., Jacobi, F., Rehm, J., Gustavsson, A., Svensson, M., Jonsson, B., . . . Steinhausen, H. C. (2011). The size and burden of mental disorders and other disorders of the brain in Europe 2010. *European Neuropsychopharmacology, 21*(9), 655-679. https://doi.org/10.1016/j.euroneuro.2011.07.018

Wolf, E. J., Miller, M. W., Sullivan, D. R., Amstadter, A. B., Mitchell, K. S., Goldberg, J., & Magruder, K. M. (2018). A classical twin study of PTSD symptoms and resilience: Evidence for a single spectrum of vulnerability to traumatic stress. *Depression and Anxiety, 35*(2), 132-139. https://doi.org/10.1002/da.22712

World Health Organization. (1993). *The ICD-10. Classification of Mental and Behavioral Disorders*. Geneva: World Health Organization.

World Health Organization. (2001). *The International Classification of Functioning, Disability and Health: ICF*. Geneva: World Health Organization.

World Health Organization. (2004). *Prevention of mental disorders: Effective interventions and policy options.* Geneva: World Health Organization.

World Health Organization. (2018). *The ICD-11 classification of mental and behavioural disorders clinical descriptions and diagnostic guidelines*. Geneva: World Health Organization.

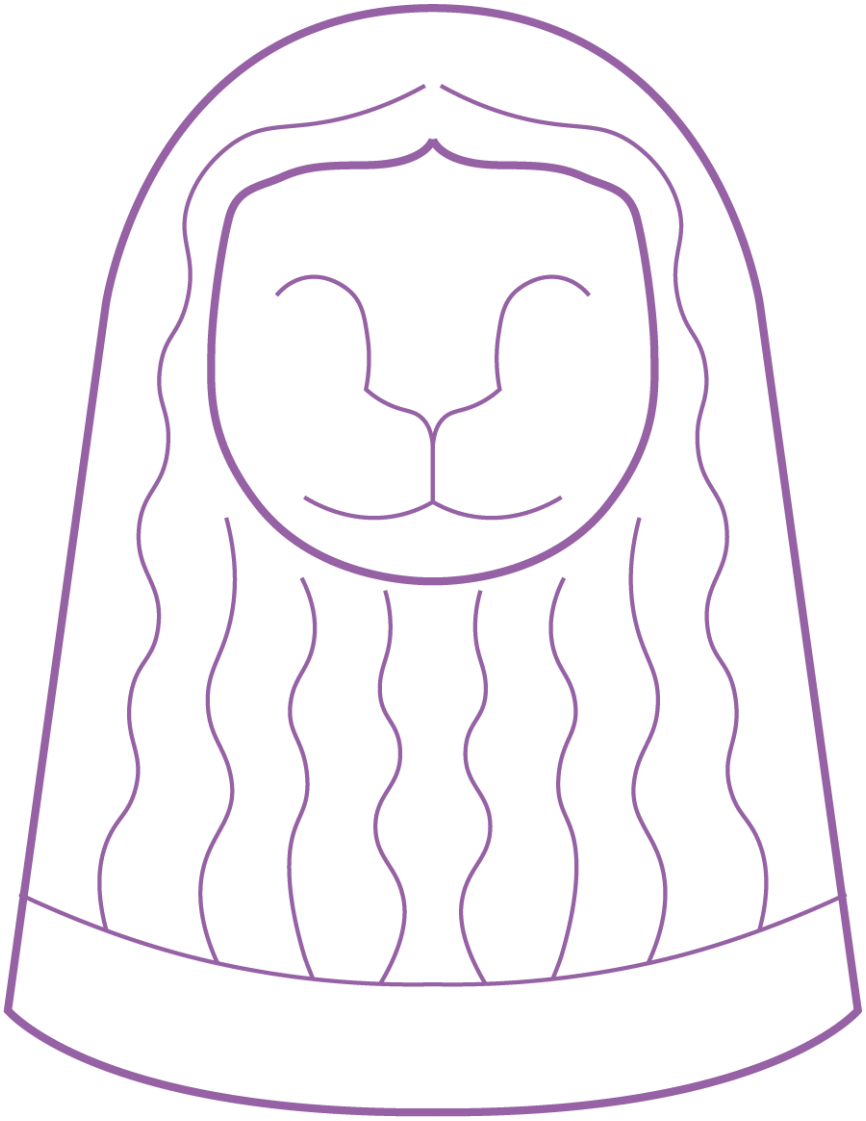
Xue-Rong, M., Qian-Bo, C., Kai, W., Kun-Ming, T., & Zhi-Jie, L. (2018). Posttraumatic stress disorder: from diagnosis to prevention. *Military Medical Research, 5*(1), 32-32. https://doi.org/10.1186/s40779-018-0179-0

Yehuda, R., Hoge, C. W., McFarlane, A. C., Vermetten, E., Lanius, R. A., Nievergelt, C. M., . . . Hyman, S. E. (2015). Post-traumatic stress disorder. *Nature Review Disease Primers, 1*, 15057. https://doi.org/10.1038/nrdp.2015.57

Ziegler, C., Dannlowski, U., Bräuer, D., Stevens, S., Laeger, I., Wittmann, H., . . . Domschke, K. (2015). Oxytocin Receptor Gene Methylation: Converging Multilevel Evidence for a Role in Social Anxiety. *Neuropsychopharmacology, 40*(6), 1528-1538. https://doi.org/10.1038/npp.2015.2

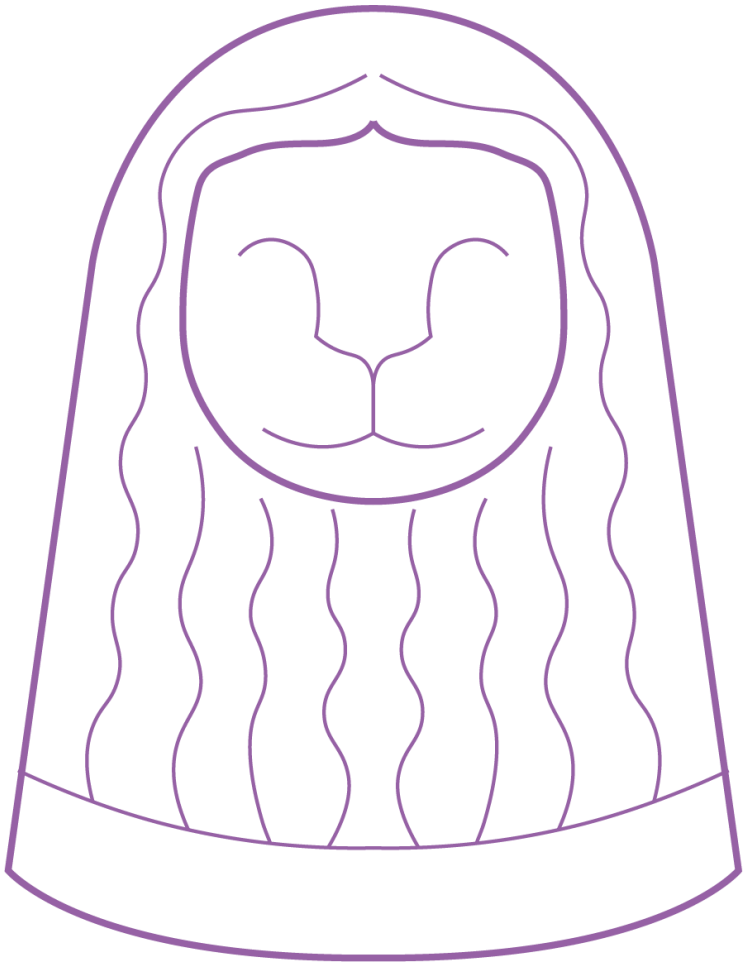
8 APPENDIX

LIST OF SCIENTIFIC PAPERS INCLUDED IN THIS THESIS



8.1 STUDY I.

VALIDITY AND RELIABILITY OF SOCIAL ANXIETY DISORDER DIAGNOSES IN THE SWEDISH NATIONAL PATIENT REGISTER



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Validity and reliability of social anxiety disorder diagnoses in the Swedish National Patient Register

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Abstract

Background: Population-based administrative registers are often used for research purposes. However, their potential usefulness depends on the validity of the registered information. This study assessed the validity of the recorded codes for social anxiety disorder (SAD), also known as social phobia, in the Swedish National Patient Register (NPR).

Methods: The personal identification numbers of 300 randomly selected individuals with a diagnosis of SAD recorded in the NPR were obtained from the Swedish National Board of Health and Welfare. The medical files of these individuals were then requested from clinics nationally. A total of 117 files were received and two independent raters reviewed each file to assess the presence or absence of SAD, according to the definition of the International Classification of Diseases, Tenth Edition (ICD-10) and the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR). When disagreements between the two raters were found, a third rater reviewed the file to establish a best estimate diagnosis. Positive predictive values (PPV) and agreement between the two initial raters (using Cohen's kappa) were calculated. Additionally, raters completed the Clinical Global Impression – Severity (CGI-S) and the Global Assessment of Functioning (GAF) rating scales for each file. Inter-rater agreement for the CGI-S and the GAF was assessed using intraclass correlation coefficients (ICC).

Results: After exclusion of files not containing sufficient information, 95 files were included in the analyses. Of these, 77 files (81.05%) were considered to be 'true positive' cases (PPV = 0.81, 95% confidence interval = 0.72–0.88). Inter-rater agreement regarding the presence or absence of SAD was substantial (κ = 0.72). CGI-S and GAF scores indicated that patients were in the moderate range of severity and functional impairment. Inter-rater agreement for the CGI-S and the GAF was moderate to good (ICC = 0.72 and ICC = 0.82, respectively).

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Conclusions: The ICD-10 codes for SAD in the Swedish NPR are generally valid and reliable, but we recommend sensitivity analyses in future register-based studies to minimise the impact of potential diagnostic misclassification. Most patients were moderately severe and impaired, suggesting that results from register-based studies of SAD may be generalizable.

Keywords: Social anxiety disorder, Social phobia, Validity, Reliability, Epidemiology,

Background

Social anxiety disorder (SAD), also commonly known as social phobia, is one of the most common psychiatric disorders, with an average worldwide lifetime prevalence of 4% [24]. The disorder is associated with substantial functional impairment [1, 18] and presents with a remarkably high degree of comorbidity [2], mainly other anxiety disorders, mood disorders, substance use disorders, and impulse control disorder [21, 24]. While much is known about the clinical features and treatment of SAD, there are important gaps in our understanding of its aetiology and long-term medical and socioeconomic consequences [4].

Swedish nationwide registers – which contain administrative records from entire population 'from cradle to grave' – and a wealth of high-quality healthcare data prospectively collected over several decades, provide unique opportunities to study risk factors as well as the long-term consequences of psychiatric disorders. In 1964, the Swedish National Board of Health and Welfare started the National Patient Register (NPR). This register contains clinical diagnoses by medical specialists, together with administrative data such as hospital or clinic of treatment, dates of admission and discharge, surgical procedures, and patient characteristics including age, sex, and place of residence [16]. At first, the NPR only compiled somatic inpatient care data from six out of 26 Swedish counties, until 1969, when it was complemented with information from psychiatric inpatient units. Since 1984, a mandatory participation for all county councils allowed to connect all data through a 10-digit unique personal identity number given to every Swedish resident, enabling cross-linkage with a range of national registers [17]. Since 2001, the register also includes all outpatient visits from private and public medical doctors (including day surgery and psychiatric care, but excluding primary care). Diagnoses in the NPR are coded according to the Swedish International Classification of Diseases (ICD) system, which was adapted from the World Health Organization ICD classification system [16].

A large variety of epidemiological and genetic studies of psychiatric disorders have been conducted using the NPR, including SAD [11, 15, 23]. However, the usefulness of this research depends on the diagnostic validity of the registered cases [19]. A review showed that the accuracy of a range of diagnostic codes in the NPR, mainly somatic diseases, ranged from 85 to 95% [16]. In psychiatry, the validity of some diagnostic codes, such as obsessive-compulsive disorder [20], chronic tic disorders [20], schizophrenia [5], bipolar disorder [22], and autism spectrum disorders [10] has been established, while the validity of other diagnoses such as SAD, has not yet been studied.

The aim of this study was to facilitate further epidemiological research using the Swedish NPR by examining the diagnostic validity and reliability of recorded diagnoses for SAD. Additionally, because it cannot be assumed that the patients in the NPR are representative of the general population of individuals with SAD, we rated their symptom severity and global functioning.

Methods

Procedures

The study was approved by the regional ethical review board in Stockholm (2012/570–31/1). A request was sent to the Swedish National Board of Health and Welfare to obtain a random sample of 300 personal identification numbers with a record of a SAD diagnosis in the NPR who had been diagnosed anywhere in Sweden. The selection of random cases was undertaken by the Swedish National Board of Health and Welfare without any control or involvement from the study researchers. No weighting or any other adjustments were used to select the cases. The number of requested cases ($n = 300$) was decided on the basis of the response rates in a previous validation study and with the aim of reaching at least 100 cases for analyses [20]. From years 1997 to 2013, a total of 31,975 SAD cases were registered in the NPR, with more than 3000 new cases per year from 2008. The graphic representation of the annual incidence of SAD cases in the NPR is shown in Fig. 1. The steep increase from 2001 was due to the inclusion of the outpatient care services in the NPR.

In order to identify records of SAD, we used the 10th revision of the ICD (ICD-10) code (F40.1), since previous revisions of the manual did not include an independent code for SAD (or 'social phobia', as named in ICD-10). The dates of registered diagnosis spanned from 1998 to 2016 for those with diagnoses in the inpatient register, and from 2001 to 2016 for those in the outpatient register. An ICD-10

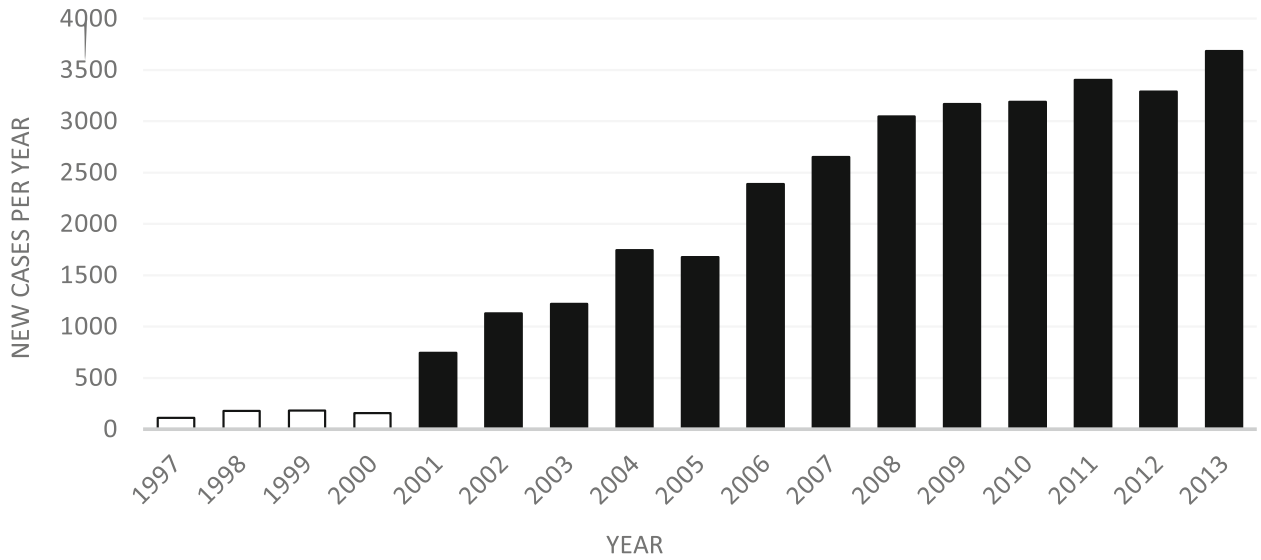

Fig. 1 Annual incidence of social anxiety disorder in the Swedish National Patient Register during the period from 1997 (introduction of the ICD-10 codes in Sweden) and 2013. *Note:* White bars represent the number of new cases diagnosed from 1997 to 2000 (inpatients only); black bars represent the number of new cases diagnosed from 2001 to 2013 (inpatients and outpatients)

diagnosis of SAD at any time during this time period was sufficient to be eligible for inclusion. The vast majority of the medical files comprised comorbid disorders and therefore contained several ICD psychiatric diagnoses codes. Administrative data including the code of the hospital or clinic where the diagnosis was given was received, together with the personal identification numbers. The full medical files of the randomly selected cases were requested from the corresponding hospitals and clinics via written letters sent through regular mail. For 22 of the 300 cases, we were not able to locate an associated clinic (e.g., the available clinic code corresponded to a clinic that was no longer operative), and therefore requests were only sent for 278 cases. In 144 of these cases, the associated clinics did not reply to the written request, and in 17 additional cases, the associated clinics declined participation. Thus, files for 117 cases were received. Of these, eight cases were excluded after inspection of the patient record, as the SAD diagnosis code was not documented in the actual received file. In a final step, 14 further cases were excluded since there was not enough information in the available material to make a diagnostic judgement (e.g., the diagnostic code was written in the patient record but clinical notes describing symptomatology were not available). Therefore, the total number of available cases for review was 95. These procedures are similar to those used in previous validation studies using the NPR [10, 20]. Figure 2 shows the flowchart of cases included in the study.

Chart review

Each of the 95 medical files available for analysis was assessed by two independent raters using a predefined score sheet (available from the corresponding author upon request). The group of raters performing the chart review was composed of 5 clinical psychologists and 2 psychiatrists, all but one with a PhD degree, with several years' experience in the assessment and treatment of anxiety disorders.

Raters were independently asked whether the information contained in the patient file was consistent with a probable diagnosis of 'social phobia' in the ICD-10. Further, since the ICD-10 classification does not contain operational diagnostic criteria but, instead, a narrative description of the disorder, raters were further asked whether the individual diagnostic criteria for 'social phobia' were also likely to be met according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR), allowing for a more systematic and operational evaluation. These judgements were largely based on the direct chart descriptions of significant levels of anxiety in social situations (e.g., nervousness in school or at work related to public speaking, anxiety when attending social events, trouble in socializing with others) and/or descriptions of avoidance of social situations due to these symptoms. Additionally, descriptions of social networks (or the lack of them), difficulties with dating or intimate relationships, evidence of academic or work underachievement or amount of sick leave linked to social anxiety symptoms were essential to assess the symptom severity and degree of functional impairment. When there were disagreements between the two raters regarding the definite or probable presence/absence of SAD, a third independent rater made a final judgement on the diagnostic status of the case. When raters considered that a case did

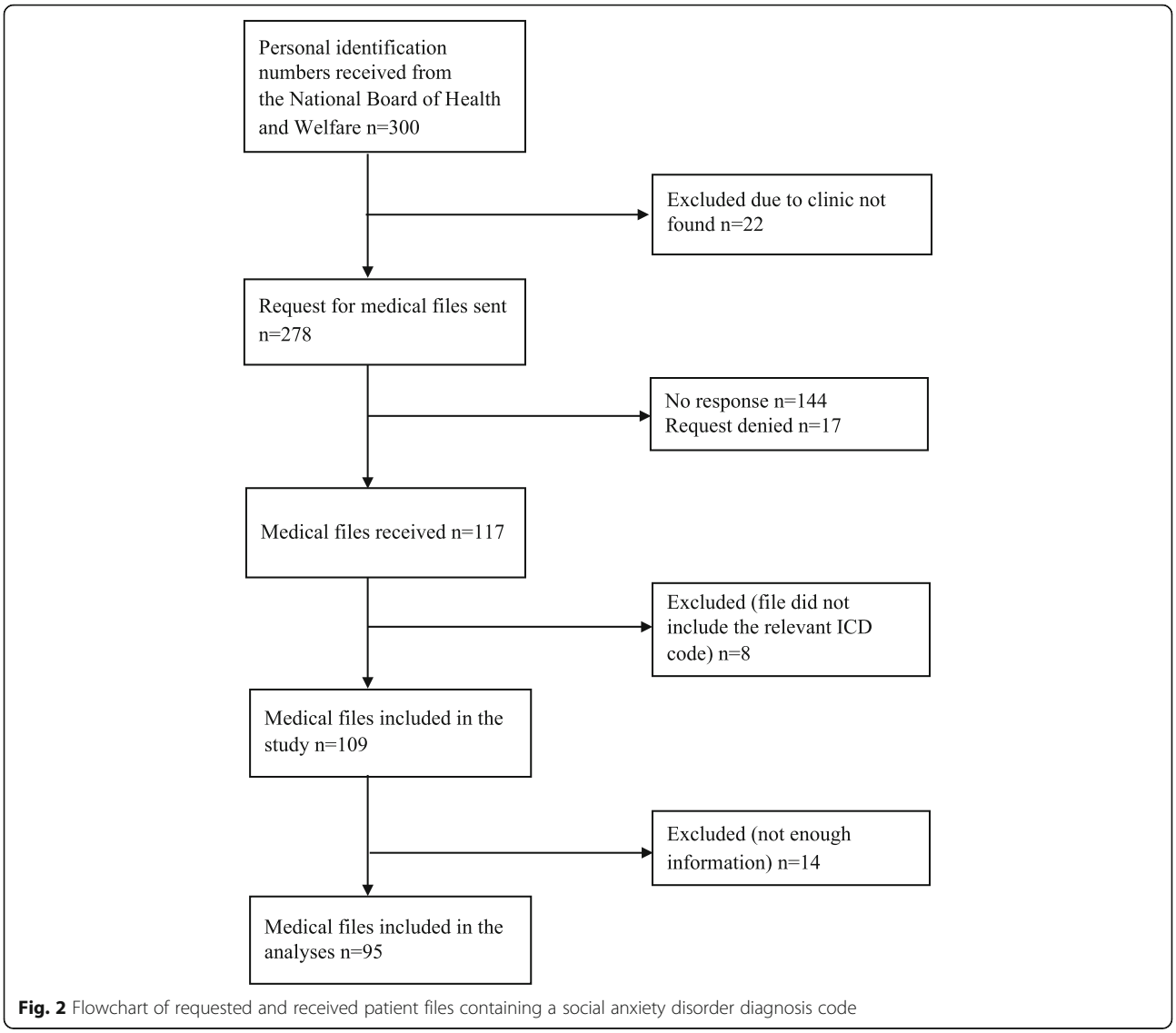

Fig. 2 Flowchart of requested and received patient files containing a social anxiety disorder diagnosis code

not meet SAD criteria (i.e., false positive), they were asked to provide the most plausible alternative diagnosis.

Further, in order to assess SAD symptom severity and global functioning in our sample of cases, raters completed the Clinical Global Impression – Severity (CGI-S) [9] and the Global Assessment of Functioning (GAF) [7] rating scales. The CGI-S is a one-item measure (*"Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?"*) which evaluates the severity of psychopathology (in this case, SAD symptoms) from 1 to 7, where 1 is 'normal' and 7 is 'among the most extremely ill patients'. This measure has been previously validated for assessing severity of SAD cases [26]. The GAF is also a one-item scale (scores ranging from 1 through 100) used by mental health professionals to subjectively rate the general social, occupational, and psychological functioning of adults [12], where the range 91–100 indicates no symptoms that impair functioning (i.e., superior functioning) and the range 1–10 implies an extremely low functioning with persistent danger for self or others. The GAF has shown good validity and reliability in the assessment of overall functioning in psychiatric patients [12]. Both of these scales are generally rated in reference to the time of the evaluation (or the week before). In this case, and for the purposes of the study, raters were asked to rate these measures averaging the severity and functioning of the patient for the whole time frame covered in each of the assessed files.

Statistical analyses

We calculated the positive predictive value (PPV) of the SAD diagnosis, that is, those cases diagnosed correctly divided by the sum of the true positives (e.g., the file was

labelled as SAD and the raters agreed on the diagnosis) and the false positives (i.e., the file was labelled as SAD but the raters did not agree with this judgement), with their corresponding 95% confidence intervals (CIs). When rater 1 and rater 2 did not agree on the diagnosis, the judgement of a third rater was used as the best estimate diagnosis against the diagnosis in the file. Inter-rater reliability was calculated using the Cohen's kappa statistic [3] with the ratings of the two initial raters. To assess the inter-rater agreement for the CGI-S and the GAF scales, intraclass correlation coefficients (ICC) with 95% CIs were calculated based on a mean-rating (k = 7), average measures, and 2-way mixed-effects model [13]. SPSS statistical package version 25 (SPSS Inc., Chicago, IL) was used for all the analyses.

Results

Validity and reliability of SAD codes in the NPR

A total of 95 cases (53 females, 56%), all from psychiatric clinics across the country, were included in the analyses. Of these, 77 (81%) were deemed as 'true positive' cases since raters considered that either the ICD-10 definition or the DSM-IV-TR diagnostic criteria for SAD were met. In most cases (94%), criteria were met according to both diagnostic systems. In the small number of cases where there was a discordance between diagnostic systems, raters considered that the ICD-10 definition was met, but not the most stringent DSM-IV-TR criteria.

The 77 'true positive' cases corresponded to a PPV of 0.81 (95% CI, 0.72–0.88). The remaining 18 cases were not considered to fulfil neither ICD-10 nor DSM-IV-TR criteria for SAD and were, therefore, considered false positive cases. The most frequent alternative diagnoses were other anxiety disorders, depression, and autism spectrum disorders (Table 1).

The Cohen's kappa between the two initial raters regarding the presence or absence of a social anxiety disorder was 0.72. Of the 7 cases where there was a disagreement between raters, four cases were added to the final number of true positives (i.e., the third rater considered that the SAD diagnosis was present) and three were deemed false positives (i.e., the third rater considered that the SAD diagnosis was absent) after the best estimate diagnosis review.

Of the 77 'true positive' cases, 71 had obtained a CGI-S and GAF score from the raters (in the remaining six cases, raters had not scored the scales and therefore this information was missing). Regarding the CGI-S, the mean score was 4.27 (sd = 0.70) for rater 1 and 4.15 (sd = 0.62) for rater 2, indicating moderate severity of the assessed cases (Fig. 3). The inter-rater agreement for the CGI-S was moderate (ICC = 0.72 [95% CI, 0.54–0.82]). For the GAF, the mean score was 52.1 (sd = 8.77) for rater 1 and 53 (sd = 9.0) for rater 2, indicating moderate difficulty in social, occupational, or school functioning (Fig. 3). The inter-rater agreement for the GAF was good (ICC = 0.82 [95% CI, 0.71–0.89]).

Discussion

The Swedish NPR includes more than 30,000 individuals with a diagnosis of SAD until 2013, and approximately 3000 new patients are added to the register each year. Therefore, the NPR constitutes a potentially unique resource for high quality epidemiological research into this disorder. However, before such research can be conducted, it is important to formally validate the corresponding ICD codes, which mainly rely on clinicians' judgements and therefore may be biased or inaccurate. Reassuringly, our results showed that the diagnostic validity of SAD in the NPR is generally good, with a PPV of 0.81 when rating the overall occurrence of SAD through chart review, the gold standard method for confirming diagnoses [25]. Further, the inter-rater agreement for the disorder was substantial [14]. The validity of the SAD diagnosis is comparable to that of other psychiatric disorders in the NPR, including bipolar disorder (PPV = 0.81–0.91) [22], schizophrenia (PPV = 0.91–1.0) [6], obsessive-compulsive disorder (PPV = 0.55–0.96) [20] or tic disorders (PPV = 0.86–0.97) [20].

In our sample, 19% of the cases were regarded as false positives (i.e., expert raters did not agree with the recorded diagnoses). The most frequent alternative

Table 1 Alternative diagnoses for false positive cases (*n* = 18)

Alternative diagnoses	Frequency
Anxiety or post-traumatic stress disorder (other than social anxiety disorder)	7
Depression	5
Autism spectrum disorder	3
Bipolar disorder	2
Eating disorder	2
Attention-deficit/hyperactivity disorder	1
Psychotic disorder	1
Borderline personality disorder	1

Note: Numbers do not add up to the total of false positive cases (n = 18) since, for some cases, raters suggested more than one alternative diagnosis

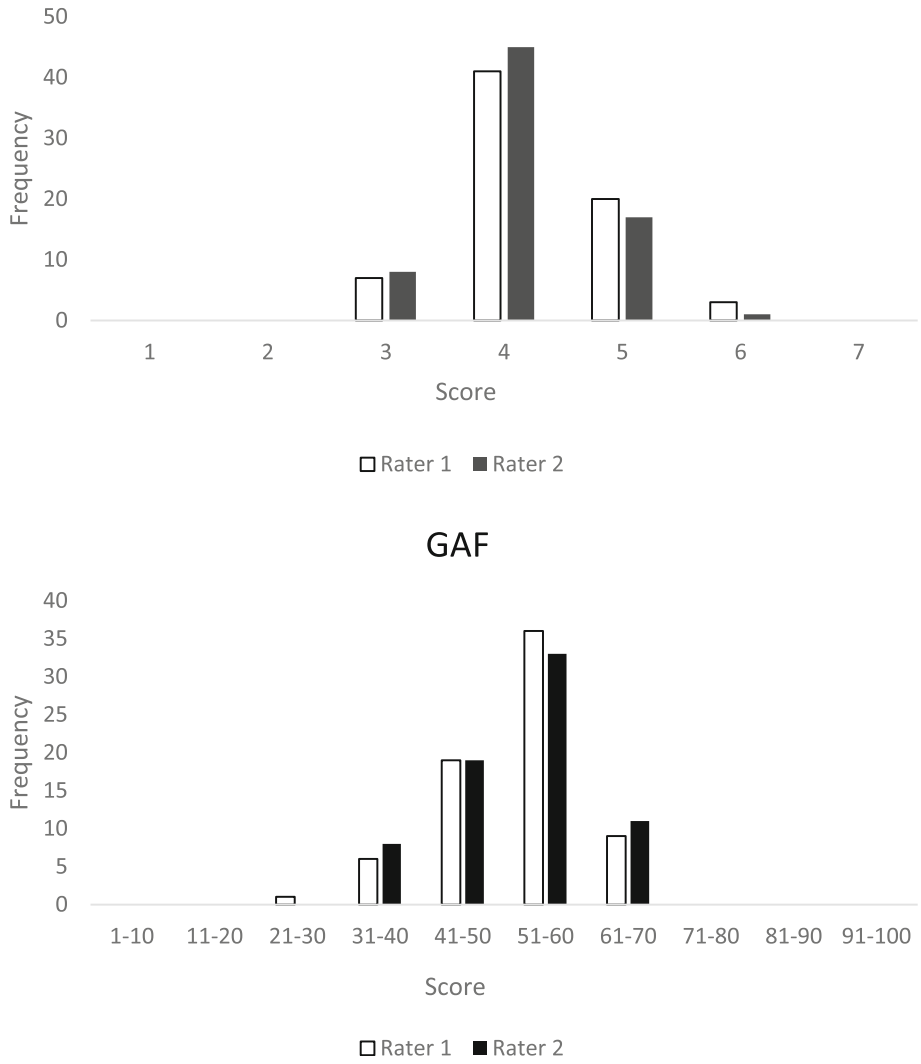

Fig. 3 Score distribution of the Clinical Global Impression – Severity (CGI-S) and Global Assessment of Functioning (GAF), by rater

diagnoses were other anxiety disorders and mood disorders, which share clinical features with SAD, as well as the underlying dimensions of distress or negative affect, shared genetic predisposition and neurobiology [8]. Since misclassification was not uncommon, we recommend that future register-based studies of SAD be always accompanied with sensitivity analyses whereby different comorbidities are systematically excluded to evaluate their impact on the outcomes of interest.

Since the NPR only includes diagnoses given by specialists, it is often assumed that patients included in this register are at the most severe end of the spectrum, potentially affecting the generalizability of the register-based results to other populations (e.g., those being seen in primary care settings). However, our severity and global functioning measures were fairly normally distributed, with most patients belonging to the moderately ill category of the CGI-S and the moderate difficulty in social, occupational or school functioning of the GAF. Thus, the results of register-based studies of SAD are likely to generalise reasonably well to other treatment-seeking populations.

The main strength of this study is the random selection of cases diagnosed with SAD from clinics placed all over the country. The medical files were meticulously evaluated by independent and skilled clinical psychologists or psychiatrists in accordance with both ICD-10 descriptions and DSM-IV-TR diagnostic criteria for SAD. However, the study is not without limitations. First, we were only able to collect and therefore assess about one third of the initially requested cases, which may suggest a potential selection bias of unknown nature. Potential differences (e.g., in demographic or clinical variables)

between the available files and those that could not be obtained could not be examined since individual information (beyond the personal identification number, the year of diagnosis, and the clinic that assigned the diagnosis) was not made available to us because it was not covered by our ethical approval for this study. However, the main reasons why we did not receive the files were mainly practical (e.g., some of the clinics did no longer exist, had confidentiality concerns or no administrative personnel was available to copy and post the files). Thus, although we cannot be certain, we believe that systematic bias is unlikely. Additionally, some of the files received did not contain sufficient information to make a decision on diagnosis; based on previous studies using similar methods [10, 20], we decided to exclude these files from the analyses, as considering them as either true positives or false positives would carry a substantial risk of reporting inaccurate PPVs. Second, because the study did not include control groups (i.e., medical records from patients without SAD), the raters were not blind to the register diagnoses, which may have increased the risk of bias towards confirming the SAD diagnoses. Lastly, raters scored the CGI and the GAF based on the chart review, without directly interviewing the patients. The validity of these scales when used in this format is unknown and, therefore, the results should only be viewed as broad clinical impressions of the patients' severity and general function. Nonetheless, the inter-rater agreement was adequate for both instruments.

Conclusions

The ICD-10 codes for SAD cases in the Swedish NPR are generally valid and reliable but we recommend sensitivity analyses in future register-based studies to minimise the impact of potential diagnostic misclassification. Most patients were moderately severe and impaired, suggesting that the results of register-based studies of SAD may be generalizable to other treatment-seeking populations.

Abbreviations

CGI-S: Clinical global impression – severity; DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; GAF: Global assessment of functioning; ICC: Intraclass correlation coefficients; ICD-10: International Classification of Diseases, Tenth Edition; NPR: National patient register; PPV: Positive predictive value; SAD: Social anxiety disorder

Acknowledgements

None.

Authors' contributions

LFC, DMC, ES, CR, and JH were involved in the conception of the research question and designed the study protocol. SK was the data manager and administrator for the project. JI, SV, MJ, JB, JH, KI, and DR were independent raters in the chart review. AVP contributed to the data management and performed the statistical analyses. AVP and LFC drafted the manuscript. LFC and DMC provided supervision. All authors contributed to the final version of the manuscript by providing substantial intellectual contributions. The authors read and approved the final manuscript.

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Availability of data and materials

No additional data are available.

Ethics approval and consent to participate

The study was approved by the regional ethical review board in Stockholm (2012/570–31/1).

Consent for publication

Not applicable.

Competing interests

JB receives book royalties from Natur & Kultur. DMC receives royalties for contributing articles to UpToDate, Wolters Kluwer Health and Elsevier. LFC receives royalties for contributing articles to UpToDate, Wolters Kluwer Health. The rest of authors declare that they have no competing interests to declare.

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References

1. Aderka IM, Hofmann SG, Nickerson A, Hermesh H, Gilboa-Schechtman E, Marom S. Functional impairment in social anxiety disorder. J Anxiety Disord. 2012;26(3):393–400. https://doi.org/10.1016/j.janxdis.2012.01.003.
2. Chartier MJ, Walker JR, Stein MB. Considering comorbidity in social phobia. Soc Psychiatry Psychiatr Epidemiol. 2003;38(12):728–34. https://doi.org/10.1007/s00127-003-0720-6.
3. Cohen. Coefficient of agreement for nominal scales. Educ Psychol Meas. 1960;20:37–46.
4. Craske MG, Stein MB. Anxiety. Lancet. 2016;388(10063):3048–59. https://doi.org/10.1016/S0140-6736(16)30381-6.
5. Dalman C, Broms J, Cullberg J, Allebeck P. Young cases of schizophrenia identified in a national inpatient register. Soc Psychiatry Psychiatr Epidemiol. 2002;37(11):527–31. https://doi.org/10.1007/s00127-002-0582-3.
6. Ekholm B, Ekholm A, Adolfsson R, Vares M, Osby U, Sedvall GC, et al. Evaluation of diagnostic procedures in Swedish patients with schizophrenia and related psychoses. Nord J Psychiatry. 2005;59(6):457–64. https://doi.org/10.1080/08039480500360906.
7. Endicott J, Spitzer RL, Fleiss JL, Cohen J. The global assessment scale: a procedure for measuring overall severity of psychiatric disturbance. JAMA Psychiat. 1976;33(6):766–71. https://doi.org/10.1001/archpsyc.1976.01770060086012.
8. Goodwin GM. The overlap between anxiety, depression, and obsessive-compulsive disorder. Dialogues Clin Neurosci. 2015;17(3):249–60.
9. Guy W, National Institute of Mental, H., Psychopharmacology Research, B., & Division of Extramural Research, P. ECDEU assessment manual for psychopharmacology : 1976. Rockville: National Institute of Mental Health; 1976.
10. Idring S, Rai D, Dal H, Dalman C, Sturm H, Zander E, et al. Autism Spectrum disorders in the Stockholm youth cohort: design, prevalence and validity (Stockholm youth cohort design). PLoS One. 2012;7(7):e41280. https://doi.org/10.1371/journal.pone.0041280.
11. Isomura K, Boman M, Ruck C, Serlachius E, Larsson H, Lichtenstein P, et al. Population-based, multi-generational family clustering study of social

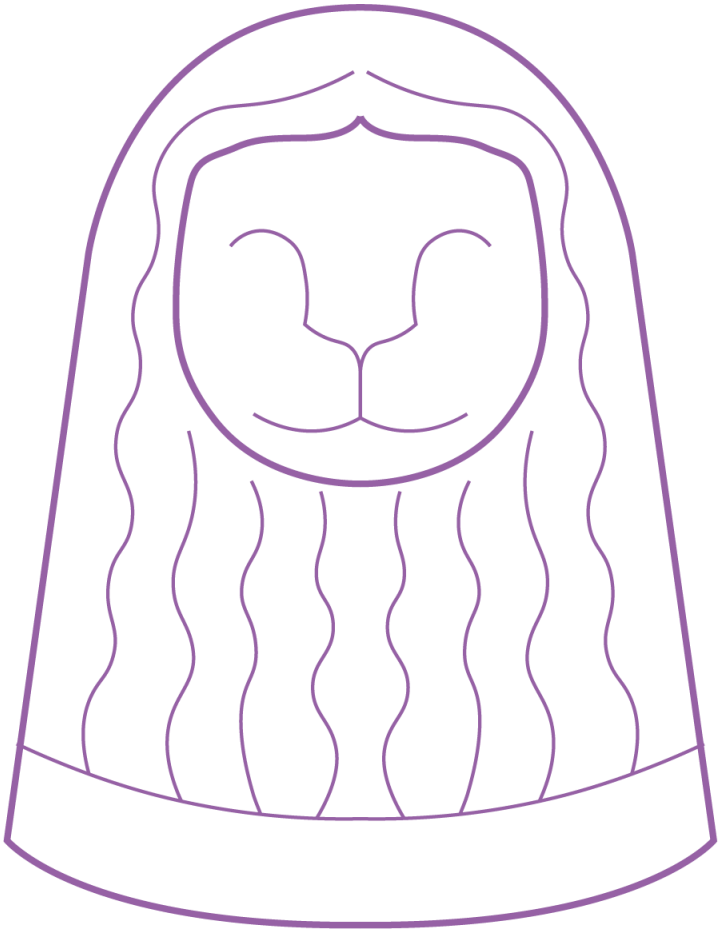
anxiety disorder and avoidant personality disorder. Psychol Med. 2015;45(8):1581–9. https://doi.org/10.1017/S0033291714002116.
12. Jones SH, Thornicroft G, Coffey M, Dunn G. A brief mental health outcome scale-reliability and validity of the global assessment of functioning (GAF). Br J Psychiatry. 1995;166(5):654–9. https://doi.org/10.1192/bjp.166.5.654.
13. Koo TK, Li MY. A guideline of selecting and reporting Intraclass correlation coefficients for reliability research. J Chiropr Med. 2016;15(2):155–63. https://doi.org/10.1016/j.jcm.2016.02.012.
14. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33(1):159–74.
15. Lichtenstein P, Halldner L, Zetterqvist J, Sjolander A, Serlachius E, Fazel S, et al. Medication for attention deficit-hyperactivity disorder and criminality. N Engl J Med. 2012;367(21):2006–14. https://doi.org/10.1056/NEJMoa1203241.
16. Ludvigsson Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011;11:450. https://doi.org/10.1186/1471-2458-11-450.
17. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. Eur J Epidemiol. 2009;24(11):659–67. https://doi.org/10.1007/s10654-009-9350-y.
18. McKnight PE, Monfort SS, Kashdan TB, Blalock DV, Calton JM. Anxiety symptoms and functional impairment: a systematic review of the correlation between the two measures. Clin Psychol Rev. 2016;45:115–30. https://doi.org/10.1016/j.cpr.2015.10.005.
19. Rosén M. National Health Data Registers: a Nordic heritage to public health. Scand J Public Health. 2002;30(2):81–5. https://doi.org/10.1177/14034948020300020101.
20. Rück C, Larsson KJ, Lind K, Perez-Vigil A, Isomura K, Sariaslan A, et al. Validity and reliability of chronic tic disorder and obsessive-compulsive disorder diagnoses in the Swedish National Patient Register. BMJ Open. 2015;5(6):e007520. https://doi.org/10.1136/bmjopen-2014-007520.
21. Ruscio AM, Brown TA, Chiu WT, Sareen J, Stein MB, Kessler RC. Social fears and social phobia in the USA: results from the National Comorbidity Survey Replication. Psychol Med. 2008;38(1):15–28. https://doi.org/10.1017/s0033291707001699.
22. Sellgren C, Landen M, Lichtenstein P, Hultman CM, Langstrom N. Validity of bipolar disorder hospital discharge diagnoses: file review and multiple register linkage in Sweden. Acta Psychiatr Scand. 2011;124(6):447–53. https://doi.org/10.1111/j.1600-0447.2011.01747.x.
23. Song H, Fang F, Tomasson G, Arnberg FK, Mataix-Cols D, Fernández de La Cruz L, et al. Association of stress-related disorders with subsequent autoimmune disease. JAMA. 2018;319(23):2388. https://doi.org/10.1001/jama.2018.7028.
24. Stein Lim CCW, Roest AM, de Jonge P, Aguilar-Gaxiola S, Al-Hamzawi A, et al. The cross-national epidemiology of social anxiety disorder: data from the world mental health survey initiative. BMC Med. 2017;15(1):143. https://doi.org/10.1186/s12916-017-0889-2.
25. Worster A, Haines T. Advanced statistics: understanding medical record review (MRR) studies. Acad Emerg Med. 2004;11(2):187–92. https://doi.org/10.1111/j.1553-2712.2004.tb01433.x.
26. Zaider TI, Heimberg RG, Fresco DM, Schneier FR, Liebowitz MR. Evaluation of the clinical global impression scale among individuals with social anxiety disorder. Psychol Med. 2003;33(4):611–22.

Publisher's Note

8.2 STUDY II.

ASSOCIATION BETWEEN SOCIAL ANXIETY DISORDER AND EDUCATIONAL ATTAINMENT:

MUCH MORE THAN JUST SHYNESS: THE IMPACT OF SOCIAL ANXIETY DISORDER ON EDUCATIONAL PERFORMANCE ACROSS THE LIFESPAN



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Much more than just shyness: the impact of social anxiety disorder on educational performance across the lifespan

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Abstract

Background. Social anxiety disorder (SAD) has been linked to academic underachievement, but previous studies had methodological limitations. We investigated the association between SAD and objective indicators of educational performance, controlling for a number of covariates and unmeasured confounders shared between siblings.

Methods. This population-based birth cohort study included 2 238 837 individuals born in Sweden between 1973 and 1997, followed-up until 2013. Within the cohort, 15 755 individuals had a recorded ICD-10 diagnosis of SAD in the Swedish National Patient Register. Logistic regression models tested the association between SAD and educational performance. We also identified 6488 families with full siblings discordant for SAD.

Results. Compared to unexposed individuals, individuals diagnosed with SAD were less likely to pass all subjects in the last year of compulsory education [adjusted odds ratios (aOR) ranging from 0.19 to 0.44] and less likely to be eligible for a vocational or academic programme in upper secondary education [aOR = 0.31 (95% confidence interval [CI] 0.30–0.33) and aOR = 0.52 (95% CI 0.50–0.55), respectively], finish upper secondary education [aOR = 0.19 (95% CI 0.19–0.20)], start a university degree [aOR = 0.47 (95% CI 0.45–0.49)], obtain a university degree [aOR = 0.35 (95% CI 0.33–0.37)], and finish postgraduate education [aOR = 0.58 (95% CI 0.43–0.80)]. Results were attenuated but remained statistically significant in adjusted sibling comparison models. When psychiatric comorbidities were taken into account, the results were largely unchanged.

Conclusions. Treatment-seeking individuals with SAD have substantially impaired academic performance throughout the formative years. Early detection and intervention are warranted to minimise the long-term socioeconomic impact of the disorder.

Introduction

Social anxiety disorder (SAD) is characterised by a persistent fear of social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others, accompanied by intense anxiety and avoidance of these social situations (American Psychiatric Association, 2013). SAD is one of the most common psychiatric disorders, affecting approximately 4% of the worldwide general population – with a slightly higher prevalence in women (Ohayon & Schatzberg, 2010) – and tends to have a chronic course (Stein et al., 2017).

Similar to other disorders with frequent onset in childhood or adolescence (Lijster et al., 2017), individuals with SAD may experience difficulties in school and thus fail to meet their full educational potential (Jangmo et al., 2019; Leach & Butterworth, 2012; Van Ameringen, Mancini, & Farvolden, 2003). Indeed, previous research has reported on the association between SAD and educational impairment. The Epidemiologic Catchment Area study reported that adults with SAD ($n = 123$) or with subthreshold SAD ($n = 248$), compared to controls of the same age without the disorder ($n = 1117$), presented significant differences in three retrospectively self-reported school performance measures, including poor grades, repeating academic years, and expulsion from school (Davidson, Hughes, George, & Blazer, 1994). Likewise, the Ontario Health Survey Mental Health Supplement showed that 38.1% of a sample of 1116 individuals with SAD did not complete high school, compared to 30.1% of those without SAD ($n = 6710$), and that a lifetime diagnosis of SAD was associated with a significantly greater likelihood of having failed an academic year and leaving school

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before graduating from high school (Stein & Kean, 2000). Similarly, in the National Comorbidity Survey, SAD was the only early-onset psychiatric disorder that predicted failure to go on to college (Kessler, 2003). In a further study including 2128 12-to-14 year-old Swedish students who completed a self-reported screening questionnaire for social anxiety, a total of 93 probable SAD cases were identified, of which 91.4% reported school impairment due to their social fear (Gren-Landell et al., 2009). Further, in a study of 3278 15-year-old Finnish adolescents, 2070 of whom were followed-up 2 years later, a different pattern of impairment was found between socially anxious boys *v.* girls, suggesting that social anxiety may have a more deleterious effect on boys' academic functioning (Ranta, La Greca, Kaltiala-Heino, & Marttunen, 2016). By contrast, a large cross-sectional Brazilian study among university students showed that women with SAD had significantly lower grades than their female control counterparts, an effect that was not observed in men (Baptista et al., 2012).

These previous studies, while valuable, generally included small sample sizes, tended to employ cross-sectional design, used retrospective self-reported measures of educational attainment, did not control for important confounders (e.g. familial factors or comorbidities), or were exclusively focused on one specific educational milestone. In this nationwide birth cohort study, we aimed to provide more comprehensive and accurate estimates of the association of SAD with educational attainment across the lifespan. To achieve this aim, we leveraged the unique Swedish population registers, which contain detailed information about psychiatric disorders diagnosed in specialist care services, as well as prospectively collected and objectively measured educational outcomes across the person's lifespan from the entire population of Sweden. Further, in order to reduce the impact of possible confounders, we adjusted for a number of covariates, controlled for psychiatric comorbidity, and employed a sibling design to control for unmeasured familial confounders. The latter provides a stricter control of genetic and environmental factors that may have a direct influence on both the exposure and the outcomes of interest.

Methods

All procedures contributing to this work comply with the Helsinki Declaration of 1975, as revised in 2008. The study was approved by the Stockholm Regional Ethical Review Board (reference number 2013/862-31/5). The requirement for informed consent was waived because the individuals included in this register-based study were de-identified.

Study population and design

Using the personal identification number assigned to all Swedish residents as a key (Ludvigsson, Otterblad-Olausson, Pettersson, & Ekbom, 2009), we linked different Swedish nationwide population-based registers, including the following: (1) the Swedish Register of Total Population (Ludvigsson et al., 2016), which contains information on sociodemographic data for all individuals in Sweden since 1968; (2) the National School Register, which holds information on individual school performance collected from all municipal and independent schools from 31 December 1988 (The Swedish National Agency for Education, 2018); (3) the Longitudinal Integration Database for Health Insurance and Labour Studies (LISA, in its Swedish acronym), which annually integrates data on the labour market, education, and social sectors from all individuals living in Sweden since 1990 (Ludvigsson, Svedberg, Olén, Bruze, & Neovius, 2019); (4) the Migration Register, which provides information about migration in and out of Sweden (Ludvigsson et al., 2016); (5) the National Patient Register (NPR), which includes inpatient hospital admissions since 1964 (1973 for psychiatric information) and outpatient care since 2001 (Ludvigsson et al., 2011); (6) the Cause of Death Register, which records information on dates and causes of all deaths since 1961, with compulsory recording nationwide (Statistics Sweden, 2013a); and (7) the Multi-Generation Register, which connects individuals born in Sweden from 1932 onwards and ever registered as living in Sweden after 1960 to their biological and adoptive parents (Ekbom, 2011), and allowed us to obtain a family pedigree for each individual in our cohort.

The initial cohort consisted of all singleton births in Sweden between 1 January 1973 and 31 December 1997, totalling 2 551 071 individuals (51.4% males), who were followed-up until 31 December 2013. As described elsewhere (Pérez-Vigil et al., 2018a; Pérez-Vigil et al., 2018b), we excluded individuals with an International Classification of Diseases (ICD) diagnosis of organic brain disorder (ICD-10 codes F00–F09) and/or intellectual disabilities (ICD-8 codes 310–315, ICD-9 codes 317–319, and ICD-10 codes F70–F79) ($n = 23\,144$). Likewise, we excluded individuals with two parents born outside Sweden or with missing data on the origin of the parents ($n = 211\,514$) (Niederkrotenthaler et al., 2014) and those who had emigrated from Sweden ($n = 105\,566$) or had died ($n = 22\,481$) before the age 15 years (i.e. prior to the expected age of graduation from compulsory education) or before year 1997 (i.e. prior to introduction of ICD-10), whichever occurred last. The final study cohort comprised 2 238 837 individuals (51.3% males).

To explore the association between SAD and each of the educational milestones under study, we created separate subcohorts, which were composed of individuals who had the necessary time to achieve the corresponding educational level (and did not die or emigrate from Sweden before the age of the predicted achievement of each educational level; see 'Statistical methods' section).

For the sibling-comparison analyses, within each subcohort we identified a subsample of families with at least two singleton full siblings (i.e. siblings of either sex sharing the same mother and father) discordant for the diagnosis of SAD.

Exposure

Treatment-seeking individuals with a lifetime diagnosis of SAD according to the ICD-10 definition (code F40.1) (World Health Organization, 1992), as recorded in the NPR, were considered exposed. In order to avoid misclassification, we set a minimal age threshold of 6 years for being diagnosed with the disorder. The ICD-10 code for SAD has been validated by our research group, showing good positive predictive values [PPV = 0.81 (95% confidence interval [CI] 0.72–0.88)] and substantial inter-rater reliability ($\kappa = 0.72$) (Vilaplana-Pérez et al., 2019). Individuals without a diagnosis of SAD were considered unexposed.

From the NPR, we also extracted all lifetime psychiatric comorbidities for the members of our cohort and organised them in five groups: (1) neuropsychiatric disorders (including pervasive developmental disorders, attention-deficit/hyperactivity disorder, Tourette syndrome and chronic tic disorder, and learning disabilities); (2) other phobic, anxiety, obsessive-compulsive, and reaction

to severe stress and adjustment disorders; (3) psychotic disorders (including schizophrenia, schizotypal, and delusional disorders); (4) affective disorders (including bipolar disorder, depressive disorders, and persistent mood disorders); and (5) substance use disorders (see online Supplementary Table S1 for details on ICD codes and age thresholds).

Outcomes

Compulsory education

The Swedish primary and lower secondary education are compulsory and take 9 years to complete (generally finished at ages 15–16). In this study, a subcohort of individuals graduating between 1998 and 2013 ($n = 1\,425\,340$) was used for this analysis. Information on individual subject grades for each participant was retrieved from the National School Register. The Swedish compulsory school system includes in total 16 compulsory subjects, for which the students are awarded the final grades upon graduation. Swedish language, English language, and mathematics are considered to be core subjects, which means that they are given extra weight in the eligibility to access upper secondary education. During the period 1998–2013, two different systems of assigning final grades were in use in Sweden and, therefore, we constructed binary variables (passed *v.* not passed) for the grades in each of 16 subjects. Furthermore, for the purposes of this study, students were also dichotomised as eligible or not eligible to access upper secondary education based on the final grades, as recorded in the National School Register. Final grades determine students' eligibility to access either vocational programmes, with a primary aim of preparing for working life, or academic programmes, which prepare for further academic studies at upper secondary school. Eligibility to access vocational programmes requires a pass grade in Swedish, English, and mathematics, and, since 2011, also requires passing five additional subjects. Academic programmes require a pass grade in Swedish, English, and mathematics, and in nine additional subjects.

Educational attainment after compulsory education

The database LISA was used to retrieve data on the following binary post-compulsory educational outcomes (recoded as achieved *v.* not achieved) for the full cohort ($n = 2\,238\,837$): finishing upper secondary education, starting a university degree, obtaining a university degree, and finishing postgraduate education (i.e. a master's or a doctoral degree).

Statistical methods

Logistic regression models were fitted to assess the association between SAD and binary educational outcomes. For each outcome, the analysis was based on the individuals who were alive and living in Sweden at the age 'old enough' to start or complete a corresponding educational level. Thus, the *likelihood of passing specific subjects* and *eligibility to progress to vocational or academic upper secondary education* was assessed among individuals who graduated from compulsory education between 1998 and 2013 and did not die or emigrate from Sweden before age 15 years. An association between diagnosis of SAD and *finishing upper secondary education* was assessed in those who were born between 1973 and 1994 (i.e. aged 19 years and above at the end of follow-up in 2013) and did not die or emigrate before the age of 19 years. Analysis of *starting a university degree* included those born between 1973 and 1992 and did not die or emigrate before the age of 21 years. *Obtaining a university degree* was assessed among individuals born between 1973 and 1988 who did not die or emigrate by the age of 25 years. Finally, the likelihood of *finishing post-graduate education* was analysed in individuals born between 1973 and 1983 who did not die or emigrate before the age of 30 years. These age cut-offs are based on the mean ages to start each educational level registered by Statistics Sweden (Statistics Sweden, 2013b). First, we ran a crude model within each subcohort for the association between SAD and the corresponding educational outcomes. In a second analysis, all models were adjusted for sex, year of birth (continuous), and maternal and paternal age at the birth of each cohort member (categorised as a 5-year increment). Results were expressed as odds ratio (OR) with 95% CIs. To account for non-independence between repeated observations within families, all analyses were clustered by mother (with information on mothers being available for all study participants), with a robust sandwich estimator of standard errors (Williams, 2000).

A fixed-effects model was implemented in the subsample of full siblings discordant for SAD, where each family was considered a stratum. By design, the model controls for familial confounders shared by full siblings, including about 50% of the genetic load and unmeasured shared environmental factors, such as socioeconomic status or stable parental traits. As above, models were adjusted for sex, birth year, and parental ages. Family identification number (based on maternal and paternal identification numbers) and a robust sandwich estimator of standard errors were used to account for non-independence of observations within families (Williams, 2000).

Sensitivity analyses were performed to assess the extent to which psychiatric comorbidities influence the association between SAD and each educational milestone. To this end, the main analyses were repeated after excluding individuals with comorbid psychiatric disorders (one group of comorbid disorders at a time).

All analyses were performed using R software, version 3.4.1 (R Development Core Team, 2017), SAS, version 9.4 (SAS Institute, Cary, NC, USA) and STATA version 15.1 (StataCorp LLC, College Station, TX, USA).

Results

Descriptive statistics

Descriptive characteristics of the study cohort are presented in Table 1. Of the 2 238 837 individuals included, 15 755 received a diagnosis of SAD, resulting in a Kaplan–Meier estimated cumulative incidence of 1.41% (95% CI 1.38–1.44) by age 40 (online Supplementary Fig. S1). The proportion of females in the SAD cohort (8706; 55.3%) was considerably larger than in the non-exposed cohort (1 081 036; 48.7%). Those with a diagnosis of SAD were more frequently diagnosed with other psychiatric disorders, compared to those without SAD (83.1% *v.* 12.3%, respectively).

Compulsory education

Analyses of the specific school subjects revealed that individuals with a diagnosis of SAD were significantly less likely to pass all subjects in the last year of compulsory education [adjusted OR (aOR) ranging from 0.19 to 0.44]. For example, individuals with SAD had 67%, 56%, and 67% lower odds of passing each of the core subjects (Swedish, English, and mathematics, respectively) (online Supplementary Table S2). The results of the sibling

Table 1. Distribution of study variables among individuals born in Sweden between 1973 and 1997, with SAD and unaffected individuals from the general population

Variable	Individuals with SAD $N = 15\,755$	Individuals without SAD $N = 2\,223\,082$
Female, *n* (%)[a]	8706 (55.3)	1 081 036 (48.3)
Age of mother at birth of individuals, mean (s.d.), years[a]	27.7 (5.4)	27.7 (5.0)
Age of father at birth of individuals, mean (s.d.), years[a]	30.7 (6.4)	30.4 (5.8)
Missing, *n* (%)	106 (0.7)	10 968 (0.5)
Comorbidity, *n* (%)		
Any	13 091 (83.1)	273 186 (12.3)
Neuropsychiatric disorders[a,b]	3938 (25)	65 019 (2.9)
Anxiety, OCD, and reaction to severe stress, and adjustment disorders[a,c]	7183 (45.6)	50 746 (2.3)
Psychotic disorders[a,d]	905 (5.7)	12 008 (0.5)
Affective disorders[a,e]	9359 (59.4)	113 941 (5.1)
Substance use disorders[a]	3760 (24)	92 046 (4.1)

OCD, obsessive-compulsive disorder; s.d., standard deviation.
[a]Statistically significant between-group difference ($p < 0.001$) determined with a χ^2 test or an independent samples, two-tailed *t* test.
[b]Includes pervasive developmental disorders, attention-deficit/hyperactivity disorder, Tourette's and chronic tic disorders and learning disabilities.
[c]Excludes social anxiety disorder.
[d]Includes schizophrenia, schizotypal, and delusional disorders.
[e]Includes bipolar disorder, depressive disorders, and persistent mood disorder.

comparison models resulted in attenuated estimates, but the results were in the same direction (aORs ranging from 0.34 to 0.66) (online Supplementary Table S3).

Individuals with SAD were significantly less likely to be eligible to access a vocational or an academic programme in upper secondary education, compared to the general population [77.3% in the exposed group were eligible for a vocational programme, compared to 91.4% in the unexposed group, aOR = 0.31 (95% CI 0.30–0.33); and 46.4% in the exposed group were eligible for an academic programme, compared to 62.7% in the unexposed group, aOR = 0.52 (95% CI 0.50–0.55)]. There were no significant sex differences in eligibility for an academic programme in the exposed group, but females with SAD were significantly less likely to be eligible for a vocational programme, compared to males with SAD [aOR for females = 0.28 (95% CI 0.26–0.30) *v.* aOR for males = 0.36 (95% CI 0.33–0.38)] (Table 2).

Similar results were obtained in the sibling comparison models, but with attenuated estimates [aOR for vocational programme = 0.53 (95% CI 0.48–0.59); aOR for academic programme = 0.63 (95% CI 0.58–0.69)] (Table 3).

Educational attainment after compulsory education

Individuals with SAD were significantly less likely to achieve each of the assessed post-compulsory educational milestones during the study period, compared to the individuals without SAD. Specifically, in the adjusted models, SAD cases had 81% lower odds of finishing upper secondary education [aOR = 0.19 (95% CI 0.19–0.20)], 53% lower odds of starting a university degree [aOR = 0.47 (95% CI 0.45–0.49)], 65% lower odds of obtaining a university degree [aOR = 0.35 (95% CI 0.33–0.37)], and 42% lower odds of achieving a post-graduate education [aOR = 0.58 (95% CI 0.43–0.80)] (Table 2). Regarding sex differences, females were significantly more impaired than males across all educational levels, except for finishing post-graduate education. The educational level presenting the largest sex difference was starting a university degree [aOR for females = 0.43 (95% CI 0.40–0.45) *v.* aOR for males = 0.54 (95% CI 0.51–0.58)].

Estimates in the sibling comparison models were again attenuated, although individuals with SAD still showed more impairment, compared to their unaffected siblings (Table 3).

Sensitivity analysis

The exclusion of individuals with different groups of comorbidities resulted in estimates similar to the ones in the main analysis (Table 4). An underpowered analysis of the impact of comorbid disorders on the likelihood of finishing post-graduate education precluded us from drawing definite conclusions. However, the observed measures of associations for the last educational milestone (although not all reaching significance) suggested the individuals with SAD to be less likely to achieve such educational outcome, regardless of comorbid disorders, thus, supporting the results from the main analysis.

Discussion

In this nationwide study, we analysed data from a large cohort of more than 2 million individuals from the Swedish population and demonstrated that individuals diagnosed with SAD are much more likely to underachieve across all levels of education. These results confirm and expand previous research, mainly based on modest sample sizes and self-reported outcomes (Davidson et al., 1994; Gren-Landell et al., 2009; Kessler, 2003; Lijster et al., 2018; Ohayon & Schatzberg, 2010; Ranta et al., 2016; Stein & Kean, 2000), by including objectively measured educational outcomes, adopting a lifespan perspective, and using a sibling comparison to control for unmeasured genetic and environmental factors that are shared by siblings.

Individuals with SAD were less likely to pass all subjects in compulsory education and were also less likely to achieve all the educational milestones under study, from compulsory education to post-graduate education, compared to individuals from the general population and also to their unaffected full siblings. The educational level that showed the greatest impairment was finishing upper secondary education; individuals with SAD had 81% lower odds of achieving this milestone. These results are in line with previously described difficulties of young people with SAD in their transition from high school to university (Kessler, 2003).

Despite the fact that more women than men, regardless of their exposure status, accessed all education levels (except for post-graduate education), women with SAD had lower odds of achieving most educational milestones, compared to men with SAD, particularly starting and obtaining a university degree. Our results are in line with those reported by Baptista et al. (2012) showing that female university students with SAD had significantly lower grades than those without SAD, which did not occur when male students with SAD were compared to those without SAD (Baptista et al., 2012). Collectively, these

Table 2. Odds ratios and corresponding 95% CIs for educational attainment among individuals with lifetime SAD, compared with unaffected individuals from the general population, stratified by gender

	Individuals with SAD *n* (%)	Individuals without SAD *n* (%)	Unadjusted model[a] OR (95% CI)	Adjusted model[b] OR (95% CI)
Compulsory education, eligibility to access upper secondary education[c]	***n* = 10 093**	***n* = 1 415 247**		
Vocational programme				
All	7803 (77.31)	1 292 842 (91.35)	**0.32 (0.31–0.34)**	**0.31 (0.30–0.33)**
Female	4543 (78.05)	638 671 (92.61)	**0.28 (0.27–0.30)**	**0.28 (0.26–0.30)**
Male	3260 (76.31)	654 171 (90.16)	**0.35 (0.33–0.38)**	**0.36 (0.33–0.38)**
Academic programme				
All	4678 (46.35)	887 028 (62.68)	**0.51 (0.49–0.54)**	**0.52 (0.50–0.55)**
Female	2739 (47.05)	439 525 (63.73)	**0.51 (0.48–0.53)**	**0.52 (0.49–0.54)**
Male	1939 (45.39)	447 503 (61.67)	**0.52 (0.49–0.55)**	**0.54 (0.50–0.57)**
Post-compulsory education				
Finishing upper secondary education[d]	***n* = 14 997**	***n* = 1 983 974**		
All	6878 (45.86)	1 602 207 (80.76)	**0.20 (0.20–0.21)**	**0.19 (0.19–0.20)**
Female	3875 (47.15)	800 591 (83.04)	**0.18 (0.17–0.19)**	**0.18 (0.17–0.19)**
Male	3003 (44.30)	801 616 (78.60)	**0.22 (0.21–0.23)**	**0.21 (0.20–0.22)**
Starting a university degree[e]	***n* = 13 901**	***n* = 1 781 080**		
All	3226 (23.21)	685 144 (38.46)	**0.48 (0.46–0.50)**	**0.47 (0.45–0.49)**
Female	1962 (26.05)	394 855 (45.78)	**0.42 (0.40–0.44)**	**0.43 (0.40–0.45)**
Male	1264 (19.85)	290 289 (31.60)	**0.54 (0.50–0.57)**	**0.54 (0.51–0.58)**
Obtaining a university degree[f]	***n* = 10 731**	***n* = 1 346 110**		
All	1187 (11.06)	350 069 (26.01)	**0.35 (0.33–0.38)**	**0.35 (0.33–0.37)**
Female	778 (13.74)	219 742 (33.80)	**0.31 (0.29–0.34)**	**0.33 (0.30–0.35)**
Male	409 (8.07)	130 327 (18.73)	**0.38 (0.34–0.42)**	**0.40 (0.36–0.45)**
Finishing post-graduate education[g]	***n* = 6680**	***n* = 892 645**		
All	40 (0.60)	10 181 (1.14)	**0.52 (0.38–0.71)**	**0.58 (0.43–0.80)**
Female	19 (0.55)	4643 (1.08)	**0.51 (0.33–0.80)**	**0.57 (0.36–0.90)**
Male	21 (0.64)	5538 (1.20)	**0.54 (0.35–0.82)**	**0.60 (0.39–0.92)**

CI, confidence interval; OR, odds ratio; SAD, social anxiety disorder.
Note: Statistically significant findings are highlighted in bold.
[a]Crude logistic regression model clustered by mother with robust standard error estimation (sandwich estimator).
[b]Multivariate logistic regression model adjusted for sex, year of birth, maternal age at birth and paternal age at birth, and clustered by mother with a robust standard error estimation (sandwich estimator). Separate analyses for males and females did not adjust for sex.
[c]Subcohort of individuals graduating compulsory school between 1998 and 2013 and not having died or emigrated from Sweden before age of 15 years.
[d]Subcohort of individuals born in 1973–1994 and not having died or emigrated from Sweden before age of 19 years.
[e]Subcohort of individuals born in 1973–1992 and not having died or emigrated from Sweden before age of 21 years.
[f]Subcohort of individuals born in 1973–1988 and not having died or emigrated from Sweden before age of 25 years.
[g]Subcohort of individuals born in 1973–1983 and not having died or emigrated from Sweden before age of 30 years.

findings suggest that women with SAD may be particularly vulnerable to scholastic underachievement.

The discordant sibling comparison resulted in attenuated estimates, indicating that part of the observed associations was explained by factors shared by siblings, including genetic and shared familial factors. Indeed, socioeconomic status, parental psychopathology, and the educational level of the parents have been previously associated with school performance in the offspring in their own right (Esch et al., 2014; Schlechter & Milevsky, 2010). Similarly, it is well known that educational attainment is heritable to a high degree (Rimfeld et al., 2018; Shakeshaft et al., 2013). However, these factors shared between siblings did not explain the whole association since SAD-affected individuals were still substantially impaired across all educational levels compared to their unaffected siblings. Similarly, systematically removing various groups of psychiatric comorbidities from our analysis did not substantially alter the results. Taken together, these results strongly suggest that SAD is associated with profound impairments in educational performance in its own right.

Given the robust associations between an individual's educational level and a wide range of health and socioeconomic outcomes later in life (Braveman & Gottlieb, 2014; OECD, 2017)

Table 3. Odds ratios and corresponding 95% CIs for educational attainment among individuals with lifetime SAD, compared with their unaffected full siblings

	Full siblings with SAD *n* (%)[c]	Full siblings without SAD *n* (%)[d]	Unadjusted model[a] OR (95% CI)	Adjusted model[b] OR (95% CI)
Compulsory education, eligibility to access upper secondary education[e]	***n* = 6488**	***n* = 9024**		
Vocational programme	5165 (79.61)	7706 (85.39)	**0.56 (0.51–0.62)**	**0.53 (0.48–0.59)**
Academic programme	3099 (47.77)	4929 (54.62)	**0.65 (0.59–0.70)**	**0.63 (0.58–0.69)**
Post-compulsory education				
Finishing upper secondary education[f]	***n* = 10 153**	***n* = 14 981**		
	4802 (47.30)	10 171 (67.89)	**0.31 (0.29–0.34)**	**0.31 (0.29–0.33)**
Starting a university degree[g]	***n* = 9121**	***n* = 13 247**		
	2313 (25.26)	4410 (33.29)	**0.55 (0.51–0.59)**	**0.54 (0.50–0.59**)
Obtaining a university degree[h]	***n* = 6471**	***n* = 8765**		
	820 (12.67)	1806 (20.60)	**0.48 (0.43–0.53)**	**0.50 (0.45–0.56)**
Finishing post graduate education[i]	***n* = 3352**	***n* = 4059**		
	23 (0.69)	39 (0.96)	0.66 (0.39–1.10)	NA

CI, confidence interval; NA, not applicable due to underpowered analysis; OR, odds ratio; SAD, social anxiety disorder.
Note: Statistically significant findings are highlighted in bold. Siblings retrieved from the same subcohort, corresponding to each educational milestone, and fulfil the same inclusion/exclusion criteria.
[a]Crude fixed-effect (i.e. conditional) logistic regression model where each family considered a stratum, with robust standard error estimation (sandwich estimator).
[b]Multivariate fixed-effect (i.e. conditional) logistic regression model, where each family considered a stratum, adjusted for sex, year of birth, maternal age at birth and paternal age at birth, with a robust standard error estimation (sandwich estimator).
[c]Individuals with SAD who have at least one full sibling without SAD; the analysis includes only full sibling pairs who are discordant be both exposure and outcome.
[d]Individuals without SAD who have at least one full sibling with SAD; the analysis includes only full sibling pairs who are discordant be both exposure and outcome.
[e]Subcohort of individuals graduating compulsory school between 1998 and 2013 and not having died or emigrated from Sweden before age of 15 years.
[f]Subcohort of individuals born in 1973–1994 and not having died or emigrated from Sweden before age of 19 years.
[g]Subcohort of individuals born in 1973–1992 and not having died or emigrated from Sweden before age of 21 years.
[h]Subcohort of individuals born in 1973–1988 and not having died or emigrated from Sweden before age of 25 years.
[i]Subcohort of individuals born in 1973–1983 and not having died or emigrated from Sweden before age of 30 years.

our results indicate that early detection and treatment of SAD should be prioritised. Whether improvement in SAD symptoms or remission from the disorder has a positive effect on educational outcomes is unknown, although it seems plausible. However, despite the existence of evidence-based treatments for the disorder (Pilling et al., 2013), only about half of individuals with SAD ever seek treatment and, when they do, it is often 10–15 years after symptom onset (Grant et al., 2005; Masia Warner et al., 2005). Moreover, parents commonly underestimate the extent of adversity experienced by young people with SAD (Ginsburg, Siqueland, Masia-Warner, & Hedtke, 2004; Masia, Klein, Storch, & Corda, 2001); anxiety symptoms are sometimes not easily observable and dismissed as just 'shyness' (Wessely, 2008). While our study is based on treatment-seeking individuals seen in specialist care, and the results may not generalise to milder forms of the disorder, they clearly indicate that SAD is much more than just shyness and can have far-reaching consequences for the individual.

Educating school staff and peers in the recognition of SAD symptoms may be a way of contributing to the early detection of SAD and facilitating referrals to relevant mental health services (Masia Warner et al., 2005, 2016; Masia Warner, Fisher, Shrout, Rathor, & Klein, 2007). For example, a two-step screening programme of social anxiety symptoms, including self-report measures and a brief phone interview with parents, proved to be effective at detecting SAD cases in a high school context (Sweeney et al., 2015). Furthermore, some clinical intervention programmes for SAD have been adapted to school contexts in order to help young people with SAD to progress in their educational goals. For instance, the Social Effectiveness Therapy for Children (SET-C) programme (Beidel, Turner, & Morris, 2000) was adapted into the 12-week Skills for Academic and Social Success (SASS) programme (Masia Warner, Colognori, & Lynch, 2018), which was shown to be superior than a non-specific counselling in reducing social anxiety and increasing school functioning in 138 high school students (Masia Warner et al., 2016). School-based interventions for SAD may have several advantages over individual treatments as they have demonstrated larger effect sizes in a recent meta-analysis (Scaini, Belotti, Ogliari, & Battaglia, 2016), in part because the school context allows for naturalistic exposures, real-world practice, and promotion of skills generalisation and better environment (Sweeney et al., 2015). The use of new technologies may also facilitate broader access to cognitive-behaviour therapy, which is efficacious but seldom available for young people and adults with SAD (Hedman et al., 2011; Nordh et al., 2017).

Strengths of the current study include the large population-based cohort with objective educational outcome data collected prospectively from nationwide administrative records, which ensured minimal risk of selection, social desirability, and recall biases. Additionally, the validity and reliability of the Swedish ICD-10 code for SAD is good (Vilaplana-Pérez et al., 2019). The follow-up period of over 20 years allowed sufficient time for the various cohorts to reach the relevant educational milestones, including post-graduate studies. The discordant sibling design provided unprecedented control of unmeasured confounders shared by full siblings. However, the study also has limitations. The study is based on treatment-seeking individuals diagnosed by specialists, which may affect the generalisability of the findings to non-treatment seeking persons or individuals

Table 4. Adjusted odds ratios and corresponding 95% CIs for educational attainment among individuals with lifetime SAD, compared with unaffected individuals from the general population, excluding different groups of comorbidities and stratified by gender

	Whole cohort	Excluding neuropsychiatric disorders	Excluding anxiety disorders	Excluding psychotic disorders	Excluding affective disorders	Excluding substance use disorders
Compulsory education, eligibility to access upper secondary education[a]						
Vocational programme						
All	**0.31 (0.30–0.33)**	**0.35 (0.33–0.38)**	**0.32 (0.30–0.34)**	**0.31 (0.30–0.33)**	**0.26 (0.25–0.28)**	**0.32 (0.30–0.33)**
Female	**0.28 (0.26–0.30)**	**0.32 (0.29–0.34)**	**0.28 (0.25–0.30)**	**0.28 (0.26–0.30)**	**0.24 (0.21–0.26)**	**0.29 (0.27–0.31)**
Male	**0.36 (0.33–0.38)**	**0.41 (0.37–0.45)**	**0.36 (0.33–0.40)**	**0.35 (0.33–0.38)**	**0.29 (0.26–0.32)**	**0.35 (0.32–0.38)**
Academic programme						
All	**0.52 (0.50–0.55)**	**0.59 (0.56–0.62)**	**0.54 (0.52–0.57)**	**0.53 (0.51–0.55)**	**0.50 (0.47–0.54)**	**0.54 (0.52–0.57)**
Female	**0.52 (0.49–0.54)**	**0.58 (0.54–0.61)**	**0.52 (0.49–0.56)**	**0.52 (0.49–0.55)**	**0.52 (0.48–0.57)**	**0.54 (0.51–0.57)**
Male	**0.54 (0.50–0.57)**	**0.61 (0.57–0.66)**	**0.57 (0.53–0.62)**	**0.54 (0.51–0.58)**	**0.48 (0.44–0.53)**	**0.55 (0.52–0.59)**
Post-compulsory education						
Finishing upper secondary education[b]						
All	**0.19 (0.19–0.20)**	**0.22 (0.21–0.23)**	**0.21 (0.20–0.22)**	**0.20 (0.19–0.20)**	**0.20 (0.19–0.21)**	**0.21 (0.20–0.22)**
Female	**0.18 (0.17–0.19)**	**0.20 (0.19–0.21)**	**0.19 (0.18–0.20)**	**0.18 (0.17–0.19)**	**0.18 (0.17–0.20)**	**0.20 (0.19–0.21)**
Male	**0.21 (0.20–0.22)**	**0.24 (0.23–0.26)**	**0.23 (0.21–0.24)**	**0.22 (0.21–0.23)**	**0.21 (0.19–0.22)**	**0.23 (0.22–0.24)**
Starting a university degree[c]						
All	**0.47 (0.45–0.49)**	**0.54 (0.52–0.56)**	**0.56 (0.53–0.59)**	**0.48 (0.46–0.50)**	**0.49 (0.46–0.52)**	**0.54 (0.52–0.57)**
Female	**0.43 (0.40–0.45)**	**0.49 (0.46–0.52)**	**0.51 (0.48–0.55)**	**0.43 (0.41–0.45)**	**0.45 (0.41–0.49)**	**0.49 (0.45–0.51)**
Male	**0.54 (0.51–0.58)**	**0.64 (0.59–0.68)**	**0.62 (0.57–0.67)**	**0.56 (0.52–0.60)**	**0.55 (0.50–0.60)**	**0.67 (0.62–0.71)**
Obtaining a university degree[d]						
All	**0.35 (0.33–0.37)**	**0.41 (0.38–0.43)**	**0.41 (0.38–0.45)**	**0.36 (0.34–0.38)**	**0.42 (0.38–0.46)**	**0.41 (0.39–0.44)**
Female	**0.33 (0.30–0.35)**	**0.37 (0.34–0.40)**	**0.39 (0.35–0.43)**	**0.33 (0.31–0.36)**	**0.39 (0.34–0.43)**	**0.37 (0.35–0.41)**
Male	**0.40 (0.36–0.45)**	**0.50 (0.45–0.55)**	**0.46 (0.40–0.52)**	**0.42 (0.38–0.47)**	**0.47 (0.41–0.54)**	**0.51 (0.45–0.57)**
Finishing post graduate education[e]						
All	**0.58 (0.43–0.80)**	**0.63 (0.45–0.88)**	0.75 (0.51–1.10)	**0.56 (0.41–0.78)**	**0.60 (0.37–0.97)**	0.75 (0.55–1.03)
Female	**0.57 (0.36–0.90)**	0.64 (0.40–1.02)	0.69 (0.38–1.25)	**0.53 (0.33–0.86)**	0.64 (0.32–1.28)	0.69 (0.44–1.09)
Male	**0.60 (0.39–0.92)**	**0.62 (0.38–0.99)**	0.79 (0.48–1.32)	**0.59 (0.38–0.93)**	0.57 (0.30–1.11)	0.81 (0.52–1.27)

Note: All odds ratios are obtained by multivariate logistic regression model adjusted for sex, year of birth, maternal age at birth and paternal age at birth and clustered by mother with robust standard error estimation (sandwich estimator). Separate analyses for males and females did not adjust for sex. Statistically significant findings are highlighted in bold. ICD codes for the disorders that constitute each group of psychiatric comorbidities are reported in online Supplementary Table S1.
[a]Subcohort of individuals graduating compulsory school between 1998 and 2013 and not having died or emigrated from Sweden before age of 15 years.
[b]Subcohort of individuals born in 1973–1994 and not having died or emigrated from Sweden before age of 19 years.
[c]Subcohort of individuals born in 1973–1992 and not having died or emigrated from Sweden before age of 21 years.
[d]Subcohort of individuals born in 1973–1988 and not having died or emigrated from Sweden before age of 25 years.
[e]Subcohort of individuals born in 1973–1983 and not having died or emigrated from Sweden before age of 30 years.

diagnosed by general practitioners or non-medical professionals (e.g. psychologists). Further, outpatient records are only available from 2001, and as the disorder does not usually require hospitalisation, the vast majority of diagnosed SAD cases in our cohort were collected from 2001 onwards. An additional limitation is that the NPR does not include measures of symptom severity, which may have a clear association with the eventual educational attainment of an individual.

Conclusion

Treatment-seeking individuals with SAD, particularly females, have substantially impaired academic performance throughout the formative years. Early detection and intervention are warranted to minimise the long-term socioeconomic impact of the disorder.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291719003908.

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References

American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders, fifth edition* (*DSM-5*®). Washington, DC: American Psychiatric Association.

Baptista, C. A., Loureiro, S. R., de Lima Osório, F., Zuardi, A. W., Magalhães, P. V., Kapczinski, F., … Crippa, J. A. S. (2012). Social phobia in Brazilian university students: Prevalence, under-recognition and academic impairment in women. *Journal of Affective Disorders*, *136*, 857–861.

Beidel, D. C., Turner, S. M., & Morris, T. L. (2000). Behavioral treatment of childhood social phobia. *Journal of Consulting and Clinical Psychology*, *68*, 1072–1080.

Braveman, P., & Gottlieb, L. (2014). The social determinants of health: It's time to consider the causes of the causes. *Public Health Reports*, *129*(Suppl 2), 19–31.

Davidson, J. T., Hughes, D. C., George, L. K., & Blazer, D. G. (1994). The boundary of social phobia: Exploring the threshold. *Archives of General Psychiatry*, *51*, 975–983.

Ekbom, A. (2011). The Swedish multi-generation register. *Methods in Molecular Biology*, *675*, 215–220.

Esch, P., Bocquet, V., Pull, C., Couffignal, S., Lehnert, T., Graas, M., … Ansseau, M. (2014). The downward spiral of mental disorders and educational attainment: A systematic review on early school leaving. *BMC Psychiatry*, *14*, 237.

Ginsburg, G. S., Siqueland, L., Masia-Warner, C., & Hedtke, K. A. (2004). Anxiety disorders in children: Family matters. *Cognitive and Behavioral Practice*, *11*, 28–43.

Grant, B. F., Hasin, D. S., Blanco, C., Stinson, F. S., Chou, S. P., Goldstein, R. B., … Huang, B. (2005). The epidemiology of social anxiety disorder in the United States: Results from the national epidemiologic survey on alcohol and related conditions. *Journal of Clinical Psychiatry*, *66*, 1351–1361.

Gren-Landell, M., Tillfors, M., Furmark, T., Bohlin, G., Andersson, G., & Svedin, C. G. (2009). Social phobia in Swedish adolescents: Prevalence and gender differences. *Social Psychiatry and Psychiatric Epidemiology*, *44*, 1–7.

Hedman, E., Andersson, G., Ljótsson, B., Andersson, E., Rück, C., Mörtberg, E., & Lindefors, N. (2011). Internet-based cognitive behavior therapy *v.* cognitive behavioral group therapy for social anxiety disorder: A randomized controlled non-inferiority trial (internet-based CBT *v.* group CBT for SAD – A RCT). *PLoS ONE*, *6*, e18001.

Jangmo, A., Stalhandske, A., Chang, Z., Chen, Q., Almqvist, C., Feldman, I., … Larsson, H. (2019). Attention-deficit/hyperactivity disorder, school performance, and effect of medication. *Journal of the American Academy of Child & Adolescent Psychiatry*, *58*, 423–432.

Kessler, R. C. (2003). The impairments caused by social phobia in the general population: Implications for intervention. *Acta Psychiatrica Scandinavica*, *108*, 19–27.

Leach, L. S., & Butterworth, P. (2012). The effect of early onset common mental disorders on educational attainment in Australia. *Psychiatry Research*, *199*, 51–57.

Lijster, J. M., Dieleman, G. C., Utens, E., Dierckx, B., Wierenga, M., Verhulst, F. C., & Legerstee, J. S. (2018). Social and academic functioning in adolescents with anxiety disorders: A systematic review. *Journal of Affective Disorders*, *230*, 108–117.

Lijster, J. M., Dierckx, B., Utens, E. M., Verhulst, F. C., Zieldorff, C., Dieleman, G. C., & Legerstee, J. S. (2017). The age of onset of anxiety disorders. *Canadian Journal of Psychiatry*, *62*, 237–246.

Ludvigsson, J. F., Almqvist, C., Bonamy, A. E., Ljung, R., Michaëlsson, K., Neovius, M., … Ye, W. (2016). Registers of the Swedish total population and their use in medical research. *European Journal of Epidemiology*, *31*, 125–136.

Ludvigsson, J. F., Andersson, E., Ekbom, A., Feychting, M., Kim, J. L., Reuterwall, C., … Olausson, P. O. (2011). External review and validation of the Swedish national inpatient register. *BMC Public Health*, *11*, 450.

Ludvigsson, J. F., Otterblad-Olausson, P., Pettersson, B. U., & Ekbom, A. (2009). The Swedish personal identity number: Possibilities and pitfalls in healthcare and medical research. *European Journal of Epidemiology*, *24*, 659–667.

Ludvigsson, J. F., Svedberg, P., Olén, O., Bruze, G., & Neovius, M. (2019). The longitudinal integrated database for health insurance and labour market studies (LISA) and its use in medical research. *European Journal of Epidemiology*, *34*, 423–437.

Masia, C., Klein, R. G., Storch, E. A., & Corda, B. (2001). School-based behavioral treatment for social anxiety disorder in adolescents: Results of a pilot study. *Journal of the American Academy of Child & Adolescent Psychiatry*, *40*, 780–786.

Masia Warner, C., Colognori, D., Brice, C., Herzig, K., Mufson, L., Lynch, C., … Klein, R. G. (2016). Can school counselors deliver cognitive-behavioral treatment for social anxiety effectively? A randomized controlled trial. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *57*, 1229–1238.

Masia Warner, C., Colognori, D., & Lynch, C. (2018). *Helping students overcome social anxiety skills for academic and social success* (*SASS*). New York: Guilford Press.

Masia Warner, C., Fisher, P. H., Shrout, P. E., Rathor, S., & Klein, R. G. (2007). Treating adolescents with social anxiety disorder in school: An attention control trial. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *48*, 676–686.

Masia Warner, C., Klein, R. G., Dent, H. C., Fisher, P. H., Alvir, J., Albano, A. M., & Guardino, M. (2005). School-based intervention for adolescents with social anxiety disorder: Results of a controlled study. *Journal of Abnormal Child Psychology*, *33*, 707–722.

Niederkrotenthaler, T., Tinghog, P., Alexanderson, K., Dahlin, M., Wang, M., Beckman, K., … Mittendorfer-Rutz, E. (2014). Future risk of labour market marginalization in young suicide attempters – A population-based prospective cohort study. *International Journal of Epidemiology*, *43*, 1520–1530.

Nordh, M., Vigerland, S., Öst, L.-G., Ljótsson, B., Mataix-Cols, D., Serlachius, E., & Högström, J. (2017). Therapist-guided internet-delivered cognitive–behavioural therapy supplemented with group exposure sessions for adolescents with social anxiety disorder: A feasibility trial. *BMJ Open*, *7*, e018345.

OECD (2017). *OECD Handbook for internationally comparative education Statistics*. Paris: OECD.

Ohayon, M. M., & Schatzberg, A. F. (2010). Social phobia and depression: Prevalence and comorbidity. *Journal of Psychosomatic Research*, *68*, 235–243.

Pérez-Vigil, A., Fernández de la Cruz, L., Brander, G., Isomura, K., Jangmo, A., Kuja-Halkola, R., … Mataix-Cols, D. (2018a). Association of Tourette syndrome and chronic tic disorders with objective indicators of educational attainment: A population-based sibling comparison study. *JAMA Neurology*, *75*, 1098–1105.

Pérez-Vigil, A., Fernández de la Cruz, L., Brander, G., Isomura, K., Jangmo, A., Feldman, I., … Mataix-Cols, D. (2018b). Association of obsessive-compulsive disorder with objective indicators of educational attainment a nationwide register-based sibling control study. *JAMA Psychiatry*, *75*, 47–55.

Pilling, S., Mayo-Wilson, E., Mavranezouli, I., Kew, K., Taylor, C., & Clark, D. M. (2013). Recognition, assessment and treatment of social anxiety disorder: Summary of NICE guidance. *BMJ*, *346*, f2541.

Ranta, K., La Greca, A. M., Kaltiala-Heino, R., & Marttunen, M. (2016). Social phobia and educational and interpersonal impairments in adolescence: A prospective study. *Child Psychiatry and Human Development*, *47*, 665–677.

Rimfeld, K., Malanchini, M., Krapohl, E., Hannigan, L. J., Dale, P. S., & Plomin, R. (2018). The stability of educational achievement across school years is largely explained by genetic factors. *NPJ Science of Learning*, *3*, 16.

Scaini, S., Belotti, R., Ogliari, A., & Battaglia, M. (2016). A comprehensive meta-analysis of cognitive-behavioral interventions for social anxiety disorder in children and adolescents. *Journal of Anxiety Disorders*, *42*, 105–112.

Schlechter, M., & Milevsky, A. (2010). Parental level of education: Associations with psychological well-being, academic achievement and reasons for pursuing higher education in adolescence. *Educational Psychologist*, *30*, 1–10.

Shakeshaft, N. G., Trzaskowski, M., McMillan, A., Rimfeld, K., Krapohl, E., Haworth, C. M. A., … Plomin, R. (2013). Strong genetic influence on a UK nationwide test of educational achievement at the end of compulsory education at age 16. *PLoS ONE*, *8*, e80341.

Statistics Sweden (2013a). *Cause of death*. Socialstyrelsen. Available at: https://www.scb.se/en/finding-statistics/statistics-by-subject-area/health-and-medical-care/causes-of-death/cause-of-death/

Statistics Sweden (2013b). Educational attainment of the population 2012. *UF37 – Educational attainment of the population*. Socialstyrelsen. Available at: https://www.scb.se/en/finding-statistics/statistics-by-subject-area/education-and-research/education-of-the-population/educational-attainment-of-the-population

Stein, M. B., & Kean, Y. M. (2000). Disability and quality of life in social phobia: Epidemiologic findings. *American Journal of Psychiatry*, *157*, 1606–1613.

Stein, M. B., Lim, C. C. W., Roest, A. M., de Jonge, P., Aguilar-Gaxiola, S., Al-Hamzawi, A., … Scott, K. M. (2017). The cross-national epidemiology of social anxiety disorder: Data from the World Mental Health Survey Initiative. *BMC Medicine*, *15*, 143.

Sweeney, C., Warner, C. M., Brice, C., Stewart, C., Ryan, J., Loeb, K. L., & McGrath, R. E. (2015). Identification of social anxiety in schools: The utility of a two-step screening process. *Contemporary School Psychology*, *19*, 268–275.

The Swedish National Agency for Education (2018). *National school register*. Statistik & utvärdering. Available at: https://www.skolverket.se/skolutveckling/statistik

Van Ameringen, M., Mancini, C., & Farvolden, P. (2003). The impact of anxiety disorders on educational achievement. *Journal of Anxiety Disorders*, *17*, 561–571.

Vilaplana-Pérez, A., Isung, J., Krig, S., Vigerland, S., Jodstelf, M., Bjureberg, J., … Fernández de la Cruz, L. (2019). Validity of social anxiety disorder in the Swedish National Patient Register. *PsyArXiv*. doi: 10.31234/osf.io/yvntq

Wessely, S. (2008). How shyness became social phobia (Book Review). *The Lancet 371*, 1063–1064.

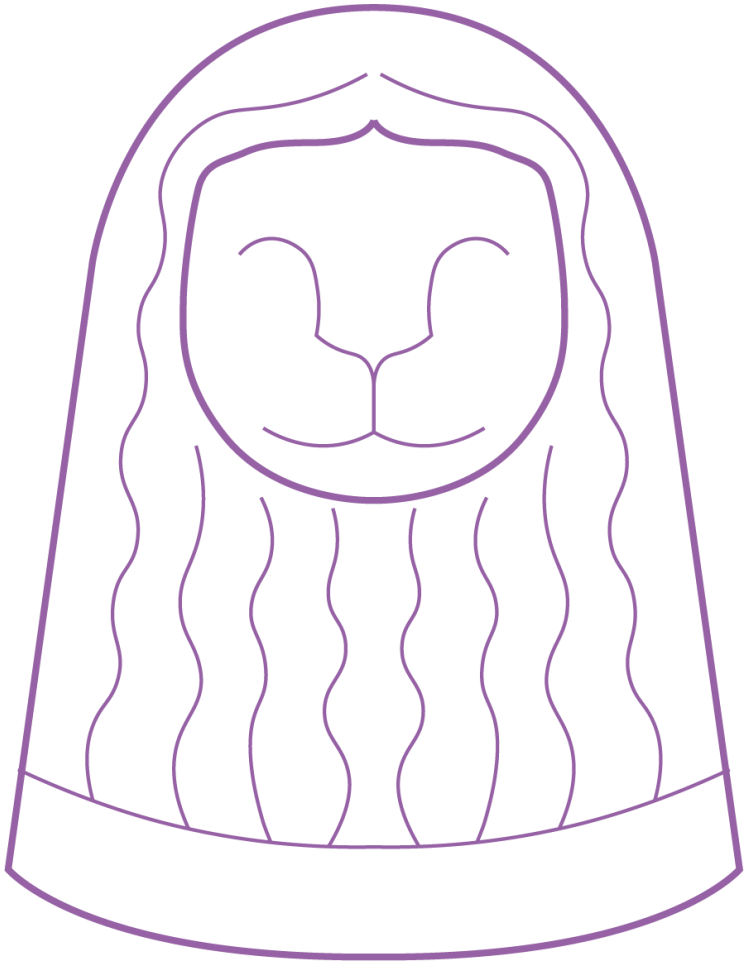
Williams, R. L. (2000). A note on robust variance estimation for cluster-correlated data. *Biometrics*, *56*, 645–646.

World Health Organization (1992). *The ICD-10 classification of mental and behavioural disorders clinical descriptions and diagnostic guidelines*. Geneva: World Health Organization.

8.3 STUDY III.

ASSOCIATION BETWEEN POSTTRAUMATIC STRESS DISORDER AND EDUCATIONAL ATTAINMENT:

ASSESSMENT OF POSTTRAUMATIC STRESS DISORDER AND EDUCATIONAL ACHIEVEMENT IN SWEDEN



Vilaplana-Pérez, A., Sidorchuk, A., Pérez-Vigil, A., Brander, G., Isomura, K., Hesselmark, E., Sevilla-Cermeño, L., Valdimarsdottir, U. A., Song, H., Jangmo, A., Kuja-Halkola, R., D'Onofrio, B., Larsson, H., Garcia-Soriano, G., Mataix-Cols, D., & Fernández de la Cruz, L. (2020). Assessment of posttraumatic stress disorder and educational achievement in Sweden. *JAMA Network Open,* 3(12):e2028477. https://doi.org/10.1001/jamanetworkopen.2020.28477

JAMA Network Open

Original Investigation | Psychiatry

Assessment of Posttraumatic Stress Disorder and Educational Achievement in Sweden

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Abstract

IMPORTANCE Posttraumatic stress disorder (PTSD) has been associated with impaired educational performance. Previous studies on the disorder could not control for important measured and unmeasured confounders.

OBJECTIVE To prospectively investigate the association between PTSD and objective indicators of educational attainment across the life span, controlling for familial factors shared by full siblings, psychiatric comorbidity, and general cognitive ability.

DESIGN, SETTING, AND PARTICIPANTS This population-based cohort study included 2 244 193 individuals born in Sweden between January 1, 1973, and December 31, 1997, who were followed-up until December 31, 2013. Clusters of full siblings were used to account for familial factors. Data analyses were conducted between December 2018 and May 2020.

EXPOSURE *International Classification of Diseases*, *Ninth Revision* and *International Statistical Classification of Diseases and Related Health Problems*, *Tenth Revision* diagnoses of PTSD in the Swedish National Patient Register.

MAIN OUTCOMES AND MEASURES Eligibility to access upper secondary education after finishing compulsory education, finishing upper secondary education, starting a university degree, and finishing a university degree.

RESULTS Of the final cohort of 2 244 193 individuals (1 151 414 [51.3%] men) included in the analysis, 1 425 326 were assessed for finishing compulsory education (919 with PTSD), 2 001 944 for finishing upper secondary education (2013 with PTSD), and 1 796 407 and 1 356 741 for starting and finishing a university degree (2243 and 2254 with PTSD, respectively). Posttraumatic stress disorder was associated with lower odds of achieving each of the educational milestones during the study period, including 82% lower odds of finishing compulsory education (adjusted odds ratio [aOR], 0.18; 95% CI, 0.15-0.20), 87% lower odds of finishing upper secondary education (aOR, 0.13; 95% CI, 0.12-0.14), 68% lower odds of starting a university degree (aOR, 0.32; 95% CI, 0.28-0.35), and 73% lower odds of finishing a university degree (aOR, 0.27; 95% CI, 0.23-0.31). Estimates in the sibling comparison were attenuated (aOR range, 0.22-0.53) but remained statistically significant. Overall, excluding psychiatric comorbidities and adjusting for the successful completion of the previous milestone and general cognitive ability did not statistically significantly alter the magnitude of the associations.

CONCLUSIONS AND RELEVANCE Posttraumatic stress disorder was associated with educational impairment across the life span, and the associations were not entirely explained by shared familial factors, psychiatric comorbidity, or general cognitive ability. This finding highlights the importance of

(continued)

Key Points

Question To what extent is posttraumatic stress disorder (PTSD) associated with impaired educational performance over and above familial factors, psychiatric comorbidity, and general cognitive ability?

Findings This population-based cohort study of 2 244 193 individuals found that those diagnosed as having PTSD were statistically significantly less likely to achieve all educational milestones, from compulsory education to finishing university, compared with individuals without the disorder independent of familial factors shared between siblings, psychiatric comorbidity, and general cognitive ability.

Meaning Findings of this study suggest that posttraumatic stress disorder is associated with lower educational performance across the life span and independent of familial factors, psychiatric comorbidity, and general cognitive ability.

+ Supplemental content

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Abstract (continued)

implementing early trauma-informed interventions in schools and universities to minimize the long-term socioeconomic consequences of academic failure in individuals with PTSD.

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Introduction

Posttraumatic stress disorder (PTSD) is a common psychiatric condition, with a lifetime prevalence of 5.6% among individuals exposed to trauma and 3.9% in the general population.[1] Known risk factors for PTSD include genetic factors, female sex, preceding somatic diseases, family history of psychiatric disorders, cumulative exposure to traumatic experiences, higher severity of the traumatic events, and low premorbid cognitive ability.[2-5] Individuals with PTSD have high rates of psychiatric comorbidity,[6] multiple adverse health consequences,[7-9] and high rates of suicide.[10,11] Posttraumatic stress disorder is associated with substantial functional impairment, including problems in relationships and family functioning[12,13] and work-related disabilities.[14] The deleterious implications of PTSD for educational performance have been suggested in a small number of primarily cross-sectional studies.[15-19] Longitudinal studies have been even scarcer but also suggest that PTSD can impair educational performance.[17,19]

Although informative, these previous studies[15-19] had several limitations, including cross-sectional designs, focus on a single educational milestone, generally small samples, self-reported educational achievements, or insufficient control of important confounders (eg, familial factors, psychiatric comorbidity, and general cognitive ability). Accounting for such potential confounders is essential because the association between PTSD and education is likely to be complex for several reasons. First, because genome-wide association studies[4,5,20,21] indicate that both PTSD vulnerability and educational achievement have a genetic component, it is possible that pleiotropic genetic effects may be at play, whereby a shared familial or genetic vulnerability may explain both the increased risk of PTSD and the poor scholastic attainment in trauma-exposed individuals. Second, PTSD is frequently comorbid with psychiatric disorders, which are in turn known to impair educational achievement.[22-25] Third, PTSD has been associated with low premorbid cognitive ability,[2,26] which correlates with educational attainment.[27,28] Given the combined association of these potential confounders, it is unclear to what extent PTSD per se disrupts education.

We aimed to investigate the association between PTSD and objective indicators of educational attainment across the life span using the Swedish national registers, which include independently and prospectively collected health care and academic data from primary to tertiary education for the whole population. To reduce the impact of possible confounders on this association, we conducted a sibling comparison, systematically evaluated the role of psychiatric comorbidities, and adjusted for a number of relevant variables.

Methods

The Stockholm Regional Ethical Review Board approved this population-based cohort study. Because all individuals included in our register-based study were deidentified, the requirement for informed consent was waived by the review board. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[29]

Data Sources and Design

We linked various Swedish nationwide registers through the unique personal identification number assigned to all residents at birth or immigration.[30] We used the Total Population Register[31] and the Cause of Death Register[32] to identify included and excluded individuals. In addition, we retrieved

information from the National Patient Register (NPR),[33] which uses codes from the *International Classification of Diseases* (*ICD*) and the Multi-generation Register,[34] that links individuals to their parents and allows identification of relatives. Information on education was gathered from the National School Register,[35] which contains information on educational attainment from all schools, and the Longitudinal Integrated Database for Health Insurance and Labour Market Studies (Swedish acronym LISA),[36] which provides annual data on education, labor market, and social sectors. We also included information from the Conscription Register,[37] which contains information about the health examination of individuals at military conscription between 1969 and 2010.

Study Population

The initial cohort consisted of all singleton births in Sweden between January 1, 1973, and December 31, 1997, totaling 2 551 071 individuals (1 306 149 men [51.2%] and 1 244 922 women [48.8%]). Because second-generation immigrants have been reported to have lower educational performance owing to language barriers (ie, their first language is different from the language spoken in the host community),[38] we excluded individuals with 2 parents born outside Sweden (or with missing data on parental origin) to control by restriction for this potential confounder. We also excluded individuals who had emigrated or died before age 15 years (the expected minimal age of graduation from compulsory education in Sweden) and individuals diagnosed as having intellectual disabilities or organic brain disorders (**Figure 1**). eTable 1 in the Supplement lists *ICD* codes and minimal age thresholds for diagnosis of psychiatric disorders. The final study cohort of 2 244 193 individuals was followed up until December 31, 2013, for their educational attainment.

Next, we defined subcohorts (**Figure 2**) to explore the association between PTSD and the educational milestones under study. Each subcohort comprised only individuals who had sufficient time to achieve every separate educational level studied and who did not emigrate or die before the expected age of achievement of each milestone (according to Statistics Sweden[39]). For the sibling comparison, we identified a subsample of families within each subcohort that comprised at least 2 singleton full siblings (ie, those sharing both parents) discordant for the diagnosis of PTSD. To adjust for general cognitive ability, we selected a subsample of men from the Conscription Register within each subcohort born in Sweden between 1973 and 1993 who were assessed for this measure at approximately age 18 years in the context of the conscription testing.

Exposure

Individuals diagnosed as having PTSD according to the *International Classification of Diseases, Ninth Revision* (*ICD-9*) (code 309B) and according to the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) (code F43.1), as recorded in the NPR (with nationwide coverage for inpatient psychiatric visits from 1973 and outpatient psychiatric visits from 2001), were considered exposed. The Swedish *ICD* codes for PTSD are valid and reliable.[40] To capture the association between PTSD and educational achievement within each subcohort, we collected the diagnosis of PTSD recorded at age 6 years or older (to avoid misclassifications) but before the expected age of completing each educational milestone. Therefore, for each subcohort, PTSD diagnoses were used to denote the exposure status if recorded between age 6 and 16 years for finishing compulsory education, between age 6 and 19 years for finishing upper secondary education, between age 6 and 21 years for starting a university degree, and between age 6 and 25 years for finishing a university degree. For each educational milestone, individuals with no PTSD diagnoses recorded in the corresponding age interval were considered unexposed.

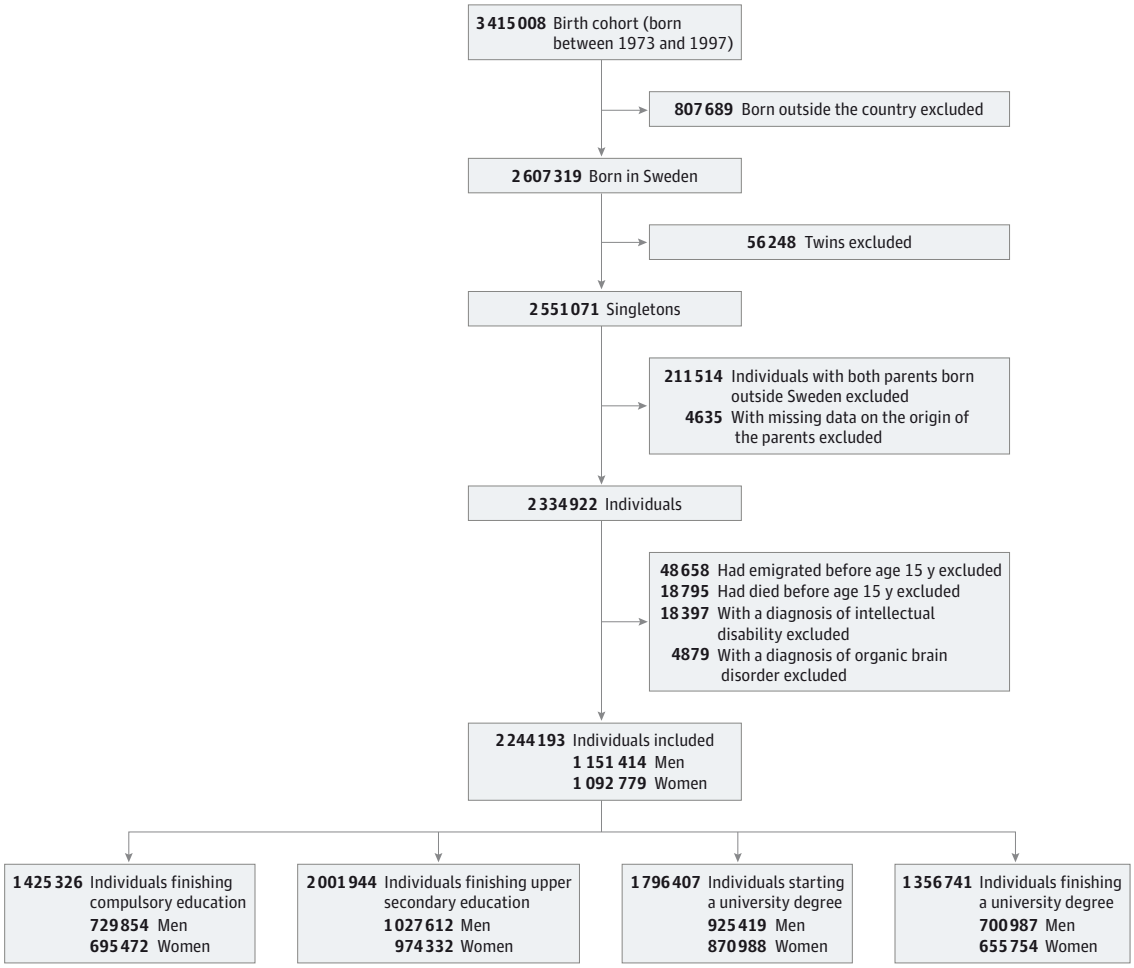
Outcomes

Compulsory Education

The Swedish primary education and lower secondary education are compulsory and take 9 years to complete (generally finished at age 15-16 years). Because of the changes introduced in 1998 in the grading system and thus in the eligibility criteria to access upper secondary education, we retrieved

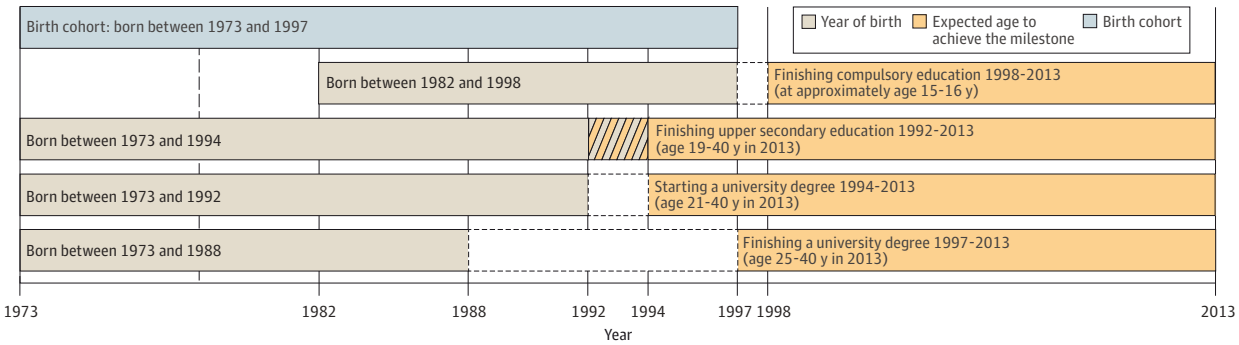
information from the National School Register only for the subcohort of individuals graduating between 1998 and 2013 (n = 1 425 326), who had comparable eligibility scores. Individuals were

Figure 1. Flowchart of the Study Population



The final study cohort comprised 2 244 193 individuals (51.3% male and 48.7% female).

Figure 2. Distribution of the Study Population



Shown is selection of subcohorts from the main birth cohort according to each educational milestone. The diagonal lines indicate the years when some individuals of the cohort were born and overlap with the oldest individuals of the cohort being old enough to finish upper secondary education. The white boxes in the middle of the figure framed by dashed lines indicate the years between when the individuals of the cohort were born and when they were not old enough to achieve the milestone.

eligible to access upper secondary education (vs not eligible) if they attained a passing grade in 3 core subjects, including Swedish, English, and mathematics (and since 2011 in 5 additional subjects[41]).

Educational Attainment After Compulsory Education

From the LISA database, we retrieved information about individual data on achieving (vs not achieving) 3 post–compulsory education levels among the members of the corresponding subcohorts. The 3 levels were finishing upper secondary education (n = 2 001 944), starting a university degree (n = 1 796 407), and finishing a university degree (n = 1 356 741).

Covariates

From the Total Population Register, we collected information on sex, birth year, and parental age at childbirth. From the NPR, we extracted lifetime information for each study participant on the following psychiatric disorders: (1) neurodevelopmental disorders (including autism spectrum disorder, attention-deficit/hyperactivity disorder, Tourette syndrome and chronic tic disorder, and learning disabilities); (2) conduct disorder; (3) phobic, anxiety, and obsessive-compulsive disorders; (4) affective disorders (including bipolar, depressive, and persistent mood disorders); (5) eating disorders; (6) psychotic disorders (including schizophrenia, schizotypal, and delusional disorders); and (7) substance use disorders (eTable 1 in the Supplement lists *ICD* codes and age thresholds). A combined "any psychiatric comorbidity" variable was also created. From the Conscription Register, we retrieved information on general cognitive ability. This measure was assessed by means of the Swedish Enlistment Battery,[42] which included subtests that measured logical, spatial, verbal, and technical abilities, generating a stanine (9-point) categorical score (mean [SD], 5 [2] points), with higher scores indicating greater abilities.

Statistical Analysis

Data analyses were conducted between December 2018 and May 2020. First, the association between PTSD and each educational outcome was assessed with logistic regression models to obtain odds ratios (ORs) and corresponding 95% CIs. Each outcome was assessed within the corresponding subcohort (ie, among the individuals who were alive and living in Sweden at the age old enough to start or complete a corresponding educational level). Crude models were followed by models adjusted for sex (binary variable), birth year (continuous variable), and maternal and paternal age at childbirth (categorized as a 5-year increment). To account for dependence between repeated observations within families, all models were clustered by the mother's identification number and a robust sandwich estimator of SEs.[43] Despite that the Swedish educational system is not linear and there are several ways of reentering the system, we conducted an additional analysis in which the models were adjusted for the outcome completed in the previous milestone (achieved vs not achieved) in an attempt to control for a potential carryover association of not passing a previous milestone.

Second, a conditional logistic regression model was used for the sibling comparison analysis within the subsample of full siblings discordant for PTSD, conditional on family identification number. By design, the model controls for familial confounders shared by full siblings (ie, about 50% of the genetic load and shared environmental factors, including socioeconomic status and stable parental traits). Within a family, unexposed siblings served as controls to the exposed siblings. Models were adjusted for the above-mentioned covariates, stratified by family identification number, and used a robust sandwich estimator of SEs.[43]

Third, we assessed the extent to which lifetime psychiatric comorbidities could explain the association between PTSD and each educational milestone. To this end, the main analyses were repeated with a stepwise restriction in which we excluded individuals with comorbid psychiatric disorders (1 group at a time). In an additional ultrastringent analysis, models were further adjusted for all psychiatric comorbidities at the same time.

Fourth, we adjusted for general cognitive ability in the subset of men within each subcohort who underwent the conscription examination. Data management and analyses were performed using SAS, version 9.4 (SAS Institute Inc) and Stata, version 15.1 (StataCorp LLC), respectively. All tests used 2-tailed statistical significance set at $P < .05$.

Results

Descriptive Statistics

The final study cohort was composed of 2 244 193 individuals (1 151 414 men [51.3%] and 1 092 779 women [48.7%]). Descriptive characteristics of the study cohorts are listed in eTable 2 in the Supplement. In total, 919 of 1 425 326 individuals (0.1%) received a diagnosis of PTSD before being eligible to access upper secondary education, 2013 of 2 001 944 individuals (0.1%) received a diagnosis of PTSD before finishing upper secondary education, 2243 of 1 796 407 individuals (0.1%) received a diagnosis of PTSD before starting a university degree, and 2254 of 1 356 741 individuals (0.2%) received a diagnosis of PTSD before finishing a university degree. Across all 4 subcohorts, the proportion of women in the PTSD cohort (range, 77.2%-81.8%) was statistically significantly larger than among the cohort of individuals without PTSD (range, 48.3%-48.8%) ($P < .001$ for all comparisons). Individuals with PTSD presented more frequently with other psychiatric comorbidity compared with those without PTSD (range, 83.4%-85.1% vs 13.3%-14.0%, respectively) ($P < .001$ for all comparisons). Among conscripted men in each of the subcohorts, general cognitive ability was statistically significantly lower for those with a diagnosis of PTSD (range, 22-237 men) compared with those without PTSD (mean [SD], 3.9 [1.8] vs 5.1 [1.9] points, respectively) ($P < .001$ for all comparisons).

Educational Milestones

Individuals with PTSD were statistically significantly less likely to complete each of the assessed educational milestones during the study period compared with individuals without PTSD. Regarding compulsory education, individuals diagnosed as having PTSD before the age of graduation (age range, 6-16 years) had 82% lower odds of being eligible to access upper secondary education compared with the individuals without a PTSD diagnosis (65.3% vs 91.3%, respectively; adjusted OR [aOR], 0.18; 95% CI, 0.15-0.20) (**Table 1**). For post–compulsory education, individuals who were diagnosed as having PTSD between ages 6 to 19 years had 87% lower odds of finishing upper secondary education (33.3% vs 80.5%, respectively; aOR, 0.13; 95% CI, 0.12-0.14) compared with those not diagnosed as having PTSD in this age interval. Similarly, individuals with a PTSD diagnosis recorded between ages 6 to 21 years had 68% lower odds of starting a university degree (15.9% vs 38.4%, respectively; aOR, 0.32; 95% CI, 0.28-0.35) compared with unexposed individuals. Those diagnosed as having PTSD between ages 6 to 25 years had 73% lower odds of finishing a university degree (8.6% vs 25.9%, respectively; aOR, 0.27; 95% CI, 0.23-0.31) compared with their unexposed counterparts. No sex differences were identified for any educational outcomes. When adjusting for completing the previous educational level, the estimates for each post–compulsory education outcome were attenuated but remained statistically significant (eTable 3 in the Supplement).

In the sibling comparison models, the estimates for all educational milestones were considerably attenuated (aOR range, 0.22-0.53) compared with those in the main analyses (ie, nonoverlapping 95% CIs). However, individuals with PTSD still had lower odds of achieving all educational outcomes compared with their unaffected siblings (**Table 2**).

For each outcome, systematically excluding individuals with different groups of psychiatric comorbidity 1 at a time did not statistically significantly alter the results (aOR range, 0.13-0.38) (**Table 3**). In addition, an ultrastringent analysis in which we further adjusted for all psychiatric comorbidity at the same time resulted in attenuated but still statistically significant associations between PTSD and impaired educational outcomes except for the outcome of starting a university degree in the sibling comparison (aOR range, 0.41-0.76) (eTable 4 in the Supplement).

When restricting analyses to conscripted men, the estimates were similar to those observed for men in the corresponding main analyses (eTable 5 in the Supplement). When models were also adjusted for the level of general cognitive ability, the estimates were slightly attenuated but remained statistically significant for all educational milestones except for the outcome of starting a

Table 1. Educational Attainment Among Individuals With PTSD Recorded Before the Corresponding Educational Milestone Compared With Unaffected Individuals From the General Population, Stratified by Sex

Variable	No. (%)[a]		OR (95% CI)[b]	
	Individuals with PTSD	Individuals without PTSD	Unadjusted model	Adjusted model[c]
Compulsory education				
Eligibility to access upper secondary education, No.	919	1 424 407	NA	NA
All	600 (65.3)	1 300 034 (91.3)	0.18 (0.16-0.21)	0.18 (0.15-0.20)
Women	468 (66.0)	642 738 (92.5)	0.16 (0.13-0.18)	0.17 (0.15-0.20)
Men	132 (62.9)	657 296 (90.1)	0.19 (0.14-0.25)	0.20 (0.15-0.26)
Post-compulsory education				
Finishing upper secondary education, No.	2013	1 999 931	NA	NA
All	670 (33.3)	1 610 765 (80.5)	0.12 (0.11-0.13)	0.13 (0.12-0.14)
Women	564 (34.3)	805 517 (82.8)	0.11 (0.10-0.12)	0.13 (0.11-0.14)
Men	106 (28.8)	805 248 (78.4)	0.11 (0.09-0.14)	0.14 (0.11-0.17)
Starting a university degree, No.	2243	1 794 164	NA	NA
All	357 (15.9)	688 378 (38.4)	0.30 (0.27-0.34)	0.32 (0.28-0.35)
Women	315 (17.2)	396 771 (45.7)	0.25 (0.22-0.28)	0.31 (0.28-0.35)
Men	42 (10.3)	291 607 (31.5)	0.25 (0.18-0.34)	0.33 (0.24-0.45)
Finishing a university degree, No.	2254	1 354 487	NA	NA
All	193 (8.6)	351 049 (25.9)	0.27 (0.23-0.31)	0.27 (0.23-0.31)
Women	172 (9.6)	220 339 (33.7)	0.21 (0.18-0.24)	0.27 (0.23-0.31)
Men	21 (4.6)	130 710 (18.7)	0.21 (0.13-0.32)	0.27 (0.18-0.42)

Abbreviations: NA, not applicable; OR, odds ratio; PTSD, posttraumatic stress disorder.

[a] The denominators for the percentages of women and men with PTSD and without PTSD are the total number of women or men exposed and unexposed, respectively, in a corresponding subcohort. For example, in the subcohort for the analysis of finishing compulsory education, of 919 individuals with PTSD, 709 were women and 210 were men. These numbers were used as denominators for calculating the sex-specific percentages for those who achieved this milestone among exposed individuals (ie, [468 ÷ 709] × 100% = 66.0% for women and [132 ÷ 210] × 100% = 62.9% for men). The total number of exposed and unexposed individuals by sex within each subcohort is reported in eTable 2 in the Supplement.

[b] All statistically significant.

[c] Adjusted for sex, year of birth, maternal age at birth, and paternal age at birth.

Table 2. Educational Attainment Among Individuals With PTSD Recorded Before the Corresponding Educational Milestone Compared With Their Unaffected Full Siblings

Variable	No. (%)[a]		OR (95% CI)[b]	
	Full siblings with PTSD	Full siblings without PTSD	Unadjusted model	Adjusted model[c]
Compulsory education				
No.	512	717	NA	NA
Eligibility to access upper secondary education	334 (65.2)	579 (80.8)	0.38 (0.28-0.51)	0.40 (0.27-0.60)
Post-compulsory education				
No.	1264	1916	NA	NA
Finishing upper secondary education	424 (33.5)	1182 (61.7)	0.24 (0.20-0.29)	0.22 (0.17-0.27)
No.	1407	2083	NA	NA
Starting a university degree	250 (17.8)	516 (24.8)	0.58 (0.48-0.71)	0.53 (0.41-0.68)
No.	1306	1881	NA	NA
Finishing a university degree	136 (10.4)	301 (16.0)	0.52 (0.40-0.67)	0.48 (0.35-0.66)

Abbreviations: NA, not applicable; OR, odds ratio; PTSD, posttraumatic stress disorder.

[a] The denominators for the percentages of siblings with PTSD and without PTSD are the total number of exposed and unexposed siblings, respectively, in a corresponding subcohort. For example, in the subcohort for the analysis of finishing compulsory education, of 512 siblings with PTSD, 334 achieved this milestone. Therefore, the percentage among exposed siblings is 65.2% ([334 ÷ 512] × 100%).

[b] All statistically significant.

[c] Adjusted for sex, year of birth, maternal age at birth, and paternal age at birth.

university degree, which was no longer statistically significant, likely because of insufficient power (aOR range, 0.19-0.68) (eTable 5 in the Supplement).

Discussion

The main finding in this population-based cohort study is that individuals with PTSD were consistently less likely to achieve all of the educational milestones studied, spanning from compulsory education to finishing a university degree, compared with individuals from the general population. Although attenuated, the results remained statistically significant after strict control for important confounders, including shared familial factors, psychiatric comorbidity, and general cognitive ability.

In this study, a preceding PTSD diagnosis seemed to be most associated with not completing upper secondary education. The odds of achieving this milestone were 87% lower for individuals with PTSD compared with those without PTSD. In other words, only 33% of individuals with PTSD completed this level vs 81% of individuals without PTSD. The latter percentage is in line with that reported in 2019 by the Organisation for Economic Cooperation and Development,[44] which indicated that 83% of adults in Sweden aged 25 to 64 years completed upper secondary education. Similarly, the results of the present study showed that individuals with PTSD had 68% lower odds of starting a university degree and 73% lower odds of finishing a university degree compared with individuals without the disorder within the same age range. These results match those of previous much smaller studies[18,19,45,46] reporting that PTSD plays a role in whether students remain enrolled in university.

In the sibling comparison, the results remained statistically significant, but the magnitude of the ORs approximately halved. This attenuation suggests that shared familial factors are important in explaining the association between PTSD and educational attainment. Therefore, it is possible that shared genetic associations may partially explain both a higher risk of PTSD and diminished educational performance in the same individuals who present both.[15,47,48] Environmental risk factors shared by siblings, such as socioeconomic status, parental psychopathology, or parental educational level (which have been previously associated with school performance in the offspring in their own right[49,50]), may be additional contributing factors.

Systematically removing various groups of psychiatric disorders from the analyses did not substantially alter the results. This finding is in contrast to a previous much smaller study[17] that reported worse educational outcomes in individuals with self-reported PTSD and alcohol use

Table 3. Educational Attainment Among Individuals With PTSD Recorded Before the Corresponding Educational Milestone Compared With Unaffected Individuals From the General Population, Excluding Various Groups of Psychiatric Comorbidities

	Adjusted OR (95% CI)[a]							
		Disorders excluded						
Variable	Whole cohort	Neurodevelopmental	Conduct	Anxiety	Affective	Eating	Psychotic	Substance use
Compulsory education								
Eligibility to access upper secondary education	0.18 (0.15-0.20)	0.21 (0.18-0.26)	0.19 (0.16-0.22)	0.18 (0.14-0.22)	0.18 (0.14-0.23)	0.17 (0.15-0.20)	0.19 (0.16-0.21)	0.19 (0.16-0.22)
Post-compulsory education								
Finishing upper secondary education	0.13 (0.12-0.14)	0.15 (0.13-0.16)	0.13 (0.12-0.15)	0.15 (0.13-0.17)	0.16 (0.14-0.18)	0.13 (0.12-0.14)	0.13 (0.12-0.15)	0.16 (0.14-0.18)
Starting a university degree	0.32 (0.28-0.35)	0.38 (0.34-0.43)	0.32 (0.29-0.36)	0.38 (0.32-0.44)	0.30 (0.25-0.36)	0.30 (0.26-0.34)	0.32 (0.29-0.36)	0.37 (0.32-0.42)
Finishing a university degree	0.27 (0.23-0.31)	0.30 (0.26-0.35)	0.27 (0.23-0.31)	0.35 (0.28-0.43)	0.29 (0.23-0.36)	0.27 (0.23-0.32)	0.29 (0.25-0.33)	0.31 (0.27-0.37)

Abbreviations: OR, odds ratio; PTSD, posttraumatic stress disorder.

[a] All statistically significant. The ORs (95% CIs) are adjusted for sex, year of birth, maternal age at birth, and paternal age at birth.

compared with those with PTSD alone. An ultrastringent analysis with adjustment for all psychiatric comorbidities at the same time resulted in somewhat attenuated estimates, but the lower odds of finishing the milestones for individuals with PTSD still held. Therefore, strict adjustment for psychiatric comorbidities did not explain the associations observed in this study.

In line with previous literature suggesting that lower premorbid intelligence is a risk factor for PTSD,[2,26] conscripted men diagnosed as having PTSD had statistically significantly lower general cognitive ability compared with those without PTSD. Therefore, adjusting for general cognitive ability was an important addition to the analyses in the present study. After adjusting for general cognitive ability, men with PTSD still had worse academic performance across the various milestones except for the association with starting a university degree, which was not statistically significant, probably because of limited power.

These results suggest that PTSD is associated with profound impairments in educational performance over and above familial factors, psychiatric comorbidity, and general cognitive ability. Although the results are not specific to PTSD—academic difficulties have also been described in other psychiatric disorders using similar methods[22-25]—the association of PTSD with educational performance seems to be more pronounced than in these other conditions, such as social anxiety disorder or obsessive-compulsive disorder.[23,25] Presumably, the core symptoms of PTSD, such as reexperiencing, hyperarousal, dissociation, and sleep problems,[51] as well as their downstream consequences on attentional or memory resources,[52] substantially interfere with the ability to function academically.

The wider implications of the results in this study are worth considering. Raising awareness in schools about the consequences that trauma can have on students could motivate early referrals to mental health services; only one-half of those with severe PTSD receive treatment, and few receive specialist mental health care.[1] Several evidence-supported training programs have been developed to integrate knowledge of trauma-related responses in teaching methods.[53,54] These programs include, for example, the Cognitive Behavioral Intervention for Trauma in Schools,[55,56] a 10-week group and individual therapy program for parents and teachers,[57] the Enhancing Resiliency Among Students Experiencing Stress (ERASE-Stress) program that has been reported to lower PTSD symptoms and depression among students,[58] and the RAP Club 12-session, school-based, trauma-informed group intervention based on cognitive behavior therapy and mindfulness strategies.[59]

Strengths and Limitations

This study has multiple strengths. First is the inclusion of a large, population-based cohort with objective educational outcome data collected prospectively from nationwide administrative records of a universal educational system. Second, the diagnostic codes for PTSD in the NPR have high validity and reliability.[40] Third, the sibling comparison design allowed us to control for unmeasured confounders shared by full siblings.[60] Fourth, we were able to strictly control for the role of psychiatric comorbidity and general cognitive ability.

The study also has limitations. First, analyses are based on treatment-seeking individuals diagnosed by specialists, which may affect the generalizability of the findings. Individuals with PTSD tend to seek help late after onset of symptoms,[61,62] which may imply a delay in diagnosis associated with misclassifications in exposed vs unexposed individuals. Furthermore, outpatient records were available only from 2001 onward. Second, the NPR does not include information on the type or number of traumatic events or any measures of symptom severity, which could potentially alter the magnitude of the observed educational impairment. Third, adjustment for general cognitive ability could be performed only in men because data for women in the Conscription Register are scarce. Whether the same results generalize to women remains to be explored. Fourth, sibling comparisons include some inherent limitations, such as potential carryover associations and environmental confounders varying between siblings.[60]

Conclusions

This study found that posttraumatic stress disorder was associated with impaired educational performance across the life span independent of familial factors shared between siblings, psychiatric comorbidity, and general cognitive ability. This finding highlights the importance of implementing trauma-informed interventions in schools and universities to minimize the long-term socioeconomic consequences of academic failure.

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REFERENCES

1. Koenen KC, Ratanatharathorn A, Ng L, et al. Posttraumatic stress disorder in the World Mental Health Surveys. *Psychol Med*. 2017;47(13):2260-2274. doi:10.1017/S0033291717000708

2. Nissen LR, Karstoft KI, Vedtofte MS, et al. Cognitive ability and risk of post-traumatic stress disorder after military deployment: an observational cohort study. *BJPsych Open*. 2017;3(6):274-280. doi:10.1192/bjpo.bp.117.005736

3. Tortella-Feliu M, Fullana MA, Pérez-Vigil A, et al. Risk factors for posttraumatic stress disorder: an umbrella review of systematic reviews and meta-analyses. *Neurosci Biobehav Rev*. 2019;107:154-165. doi:10.1016/j.neubiorev.2019.09.013

4. Gelernter J, Sun N, Polimanti R, et al; Department of Veterans Affairs Cooperative Studies Program (#575B) and Million Veteran Program. Genome-wide association study of post-traumatic stress disorder reexperiencing symptoms in >165,000 US veterans. *Nat Neurosci*. 2019;22(9):1394-1401. doi:10.1038/s41593-019-0447-7

5. Nievergelt CM, Maihofer AX, Klengel T, et al. International meta-analysis of PTSD genome-wide association studies identifies sex- and ancestry-specific genetic risk loci. *Nat Commun*. 2019;10(1):4558. doi:10.1038/s41467-019-12576-w

6. Pietrzak RH, Goldstein RB, Southwick SM, Grant BF. Prevalence and axis I comorbidity of full and partial posttraumatic stress disorder in the United States: results from wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions. *J Anxiety Disord*. 2011;25(3):456-465. doi:10.1016/j.janxdis.2010.11.010

7. Song H, Sieurin J, Wirdefeldt K, et al. Association of stress-related disorders with subsequent neurodegenerative diseases. *JAMA Neurol*. 2020;77(6):700-709. doi:10.1001/jamaneurol.2020.0117

8. Song H, Fang F, Arnberg FK, et al. Stress related disorders and risk of cardiovascular disease: population based, sibling controlled cohort study. *BMJ*. 2019;365:l1255. doi:10.1136/bmj.l1255

9. Song H, Fall K, Fang F, et al. Stress related disorders and subsequent risk of life threatening infections: population based sibling controlled cohort study. *BMJ*. 2019;367:l5784. doi:10.1136/bmj.l5784

10. Gradus JL. Posttraumatic stress disorder and death from suicide. *Curr Psychiatry Rep*. 2018;20(11):98. doi:10.1007/s11920-018-0965-0

11. Gradus JL, Antonsen S, Svensson E, Lash TL, Resick PA, Hansen JG. Trauma, comorbidity, and mortality following diagnoses of severe stress and adjustment disorders: a nationwide cohort study. *Am J Epidemiol*. 2015;182(5):451-458. doi:10.1093/aje/kwv066

12. Birkley EL, Eckhardt CI, Dykstra RE. Posttraumatic stress disorder symptoms, intimate partner violence, and relationship functioning: a meta-analytic review. *J Trauma Stress*. 2016;29(5):397-405. doi:10.1002/jts.22129

13. Taft CT, Watkins LE, Stafford J, Street AE, Monson CM. Posttraumatic stress disorder and intimate relationship problems: a meta-analysis. *J Consult Clin Psychol*. 2011;79(1):22-33. doi:10.1037/a0022196

14. Wald J, Taylor S. Work impairment and disability in posttraumatic stress disorder: a review and recommendations for psychological injury research and practice. *Psychol Inj Law*. 2009;2(3):254-262. doi:10.1007/s12207-009-9059-y

15. Polimanti R, Ratanatharathorn A, Maihofer AX, et al; Psychiatric Genomics Consortium Posttraumatic Stress Disorder Working Group. Association of economic status and educational attainment with posttraumatic stress disorder: a mendelian randomization study. *JAMA Netw Open*. 2019;2(5):e193447. doi:10.1001/jamanetworkopen.2019.3447

16. Morissette SB, Ryan-Gonzalez C, Yufik T, et al. The effects of posttraumatic stress disorder symptoms on educational functioning in student veterans. *Psychol Serv*. Published online June 13, 2019. doi:10.1037/ser0000356

17. Bachrach RL, Read JP. The role of posttraumatic stress and problem alcohol involvement in university academic performance. *J Clin Psychol*. 2012;68(7):843-859. doi:10.1002/jclp.21874

18. Pereira JL, Guedes-Carneiro GM, Netto LR, et al; Trauma Anxiety Disorders Study Group–Universidade Federal da Bahia. Types of trauma, posttraumatic stress disorder, and academic performance in a population of university students. *J Nerv Ment Dis*. 2018;206(7):507-512. doi:10.1097/NMD.0000000000000842

19. Boyraz G, Granda R, Baker CN, Tidwell LL, Waits JB. Posttraumatic stress, effort regulation, and academic outcomes among college students: a longitudinal study. *J Couns Psychol*. 2016;63(4):475-486. doi:10.1037/cou0000102

20. Selzam S, Krapohl E, von Stumm S, et al. Predicting educational achievement from DNA. *Mol Psychiatry*. 2017;22(2):267-272. doi:10.1038/mp.2016.107

21. Lee JJ, Wedow R, Okbay A, et al; 23andMe Research Team; COGENT (Cognitive Genomics Consortium); Social Science Genetic Association Consortium. Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals. *Nat Genet*. 2018;50(8):1112-1121. doi:10.1038/s41588-018-0147-3

22. Dalsgaard S, McGrath J, Østergaard SD, et al. Association of mental disorder in childhood and adolescence with subsequent educational achievement. *JAMA Psychiatry*. 2020;77(8):797-805. doi:10.1001/jamapsychiatry.2020.0217

23. Vilaplana-Pérez A, Pérez-Vigil A, Sidorchuk A, et al. Much more than just shyness: the impact of social anxiety disorder on educational performance across the lifespan. *Psychol Med*. Published online January 7, 2020. doi:10.1017/S0033291719003908

24. Pérez-Vigil A, Fernández de la Cruz L, Brander G, et al. Association of Tourette syndrome and chronic tic disorders with objective indicators of educational attainment: a population-based sibling comparison study. *JAMA Neurol*. 2018;75(9):1098-1105. doi:10.1001/jamaneurol.2018.1194

25. Pérez-Vigil A, Fernández de la Cruz L, Brander G, et al. Association of obsessive-compulsive disorder with objective indicators of educational attainment: a nationwide register-based sibling control study. *JAMA Psychiatry*. 2018;75(1):47-55. doi:10.1001/jamapsychiatry.2017.3523

26. Kremen WS, Koenen KC, Boake C, et al. Pretrauma cognitive ability and risk for posttraumatic stress disorder: a twin study. *Arch Gen Psychiatry*. 2007;64(3):361-368. doi:10.1001/archpsyc.64.3.361

27. Morris T, Dorling D, Davey Smith G. How well can we predict educational outcomes? examining the roles of cognitive ability and social position in educational attainment. *Contemp Soc Sci*. 2016;11(2-3):154-168. doi:10.1080/21582041.2016.1138502

28. Allegrini AG, Selzam S, Rimfeld K, von Stumm S, Pingault JB, Plomin R. Genomic prediction of cognitive traits in childhood and adolescence. *Mol Psychiatry*. 2019;24(6):819-827. doi:10.1038/s41380-019-0394-4

29. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Prev Med*. 2007;45(4):247-251. doi:10.1016/j.ypmed.2007.08.012

30. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol*. 2009;24(11):659-667. doi:10.1007/s10654-009-9350-y

31. Ludvigsson JF, Almqvist C, Bonamy AK, et al. Registers of the Swedish total population and their use in medical research. *Eur J Epidemiol*. 2016;31(2):125-136. doi:10.1007/s10654-016-0117-y

32. Brooke HL, Talbäck M, Hörnblad J, et al. The Swedish Cause of Death Register. *Eur J Epidemiol*. 2017;32(9):765-773. doi:10.1007/s10654-017-0316-1

33. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish National Inpatient Register. *BMC Public Health*. 2011;11:450. doi:10.1186/1471-2458-11-450

34. Ekbom A. The Swedish Multi-generation Register. *Methods Mol Biol*. 2011;675:215-220. doi:10.1007/978-1-59745-423-0_10

35. The Swedish National Agency for Education. National School Register. Statistik & utvärdering. Published 2018. Accessed October 5, 2018. https://www.skolverket.se/

36. Ludvigsson JF, Svedberg P, Olén O, Bruze G, Neovius M. The Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA) and its use in medical research. *Eur J Epidemiol*. 2019;34(4):423-437. doi:10.1007/s10654-019-00511-8

37. Whitley E, Batty GD, Gale CR, Deary IJ, Tynelius P, Rasmussen F. Intelligence in early adulthood and subsequent risk of unintentional injury over two decades: cohort study of 1 109 475 Swedish men. *J Epidemiol Community Health*. 2010;64(5):419-425. doi:10.1136/jech.2009.100669

38. Organisation for Economic Cooperation and Development. Helping immigrant students to succeed at school—and beyond. Published 2015. Accessed October 27, 2020. https://www.oecd.org/education/Helping-immigrant-students-to-succeed-at-school-and-beyond.pdf

39. Statistics Sweden. Educational attainment of the population 2013. Socialstyrelsen. UF037–Educational attainment of the population website. Published October 23, 2014. Accessed November 1, 2018. http://share.scb.se/ov9993/data/publikationer/statistik/uf/uf0317/2013a01/uf0317_2013a01_sm_uf10sm1401.pdf

40. Hollander AC, Askegård K, Iddon-Escalante C, Holmes EA, Wicks S, Dalman C. Validation study of randomly selected cases of PTSD diagnoses identified in a Swedish regional database compared with medical records: is the validity sufficient for epidemiological research? *BMJ Open*. 2019;9(12):e031964. doi:10.1136/bmjopen-2019-031964

41. The Education Act-Skollag. (2010:800), Ministry of Education, June 23, 2010. Accessed October 31, 2020. https://www.riksdagen.se/sv/dokument-lagar/dokument/svensk-forfattningssamling/skollag-2010800_sfs-2010-800

42. Mårdberg B, Carlstedt B. Swedish Enlistment Battery (SEB): construct validity and latent variable estimation of cognitive abilities by the CAT-SEB. *Int J Selection Assessment*. 1998;6(2):107-114. doi:10.1111/1468-2389.00079

43. Williams RL. A note on robust variance estimation for cluster-correlated data. *Biometrics*. 2000;56(2):645-646. doi:10.1111/j.0006-341X.2000.00645.x

44. Organisation for Economic Cooperation and Development. *Education at a Glance 2019: OECD Indicators*. OECD Publishing; 2019.

45. Boyraz G, Horne SG, Owens AC, Armstrong AP. Academic achievement and college persistence of African American students with trauma exposure. *J Couns Psychol*. 2013;60(4):582-592. doi:10.1037/a0033672

46. Auerbach RP, Alonso J, Axinn WG, et al. Mental disorders among college students in the World Health Organization World Mental Health Surveys. *Psychol Med*. 2016;46(14):2955-2970. doi:10.1017/S0033291716001665

47. Rimfeld K, Malanchini M, Krapohl E, Hannigan LJ, Dale PS, Plomin R. The stability of educational achievement across school years is largely explained by genetic factors. *NPJ Sci Learn*. 2018;3(1):16. doi:10.1038/s41539-018-0030-0

48. Shakeshaft NG, Trzaskowski M, McMillan A, et al. Strong genetic influence on a UK nationwide test of educational achievement at the end of compulsory education at age 16. *PLoS One*. 2013;8(12):e80341. doi:10.1371/journal.pone.0080341

49. Esch P, Bocquet V, Pull C, et al. The downward spiral of mental disorders and educational attainment: a systematic review on early school leaving. *BMC Psychiatry*. 2014;14(1):237. doi:10.1186/s12888-014-0237-4

50. Schlechter M, Milevsky A. Parental level of education: associations with psychological well-being, academic achievement and reasons for pursuing higher education in adolescence. *Educ Psychol*. 2010;30(1):1-10. doi:10.1080/01443410903326084

51. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Association; 2013.

52. Scott JC, Matt GE, Wrocklage KM, et al. A quantitative meta-analysis of neurocognitive functioning in posttraumatic stress disorder. *Psychol Bull*. 2015;141(1):105-140. doi:10.1037/a0038039

53. Rossen EA, Hull R. *Supporting and Educating Traumatized Students: A Guide for School-Based Professionals*. Oxford University Press; 2013.

54. Porche MV, Costello DM, Rosen-Reynoso M. Adverse family experiences, child mental health, and educational outcomes for a national sample of students. *School Mental Health*. 2016;8(1):44-60. doi:10.1007/s12310-016-9174-3

55. Jaycox LH, Kataoka SH, Stein BD, Langley AK, Wong M. Cognitive behavioral intervention for trauma in schools. *J Applied School Psychol*. 2012;28(3):239-255. doi:10.1080/15377903.2012.695766

56. Hoover SA, Sapere H, Lang JM, Nadeem E, Dean KL, Vona P. Statewide implementation of an evidence-based trauma intervention in schools. *Sch Psychol Q*. 2018;33(1):44-53. doi:10.1037/spq0000248

57. Vona P, Wilmoth P, Jaycox LH, et al. A web-based platform to support an evidence-based mental health intervention: lessons from the CBITS web site. *Psychiatr Serv*. 2014;65(11):1381-1384. doi:10.1176/appi.ps.201300512

58. Berger R, Gelkopf M. School-based intervention for the treatment of tsunami-related distress in children: a quasi-randomized controlled trial. *Psychother Psychosom*. 2009;78(6):364-371. doi:10.1159/000235976

59. Mendelson T, Tandon SD, O'Brennan L, Leaf PJ, Ialongo NS. Brief report: moving prevention into schools: the impact of a trauma-informed school-based intervention. *J Adolesc*. 2015;43:142-147. doi:10.1016/j.adolescence.2015.05.017

60. D'Onofrio BM, Lahey BB, Turkheimer E, Lichtenstein P. Critical need for family-based, quasi-experimental designs in integrating genetic and social science research. *Am J Public Health*. 2013;103(suppl 1):S46-S55. doi:10.2105/AJPH.2013.301252

61. Wang PS, Lane M, Olfson M, Pincus HA, Wells KB, Kessler RC. Twelve-month use of mental health services in the United States: results from the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62(6):629-640. doi:10.1001/archpsyc.62.6.629

62. Smith JR, Workneh A, Yaya S. Barriers and facilitators to help-seeking for individuals with posttraumatic stress disorder: a systematic review. *J Trauma Stress*. 2020;33(2):137-150. doi:10.1002/jts.22456

SUPPLEMENT.

eTable 1. Diagnostic Groups With International Classification of Diseases, Version 8 (ICD-8), 9 (ICD-9), and 10 (ICD-10) Codes and Age Thresholds for Psychiatric Disorders and Excluded Diagnoses

eTable 2. Distribution of Study Covariates Among Individuals With Post-traumatic Stress Disorder (PTSD) and Unaffected Individuals From the General Population Within Each Subcohort

eTable 3. Odds Ratios (OR) and Corresponding 95% CIs for Educational Attainment Among Individuals With Post-traumatic Stress Disorder (PTSD) Recorded Before the Corresponding Educational Milestone, Compared With Unaffected Individuals From the General Population, Stratified by Gender and Controlled for the Achievement at Previous Educational Level

eTable 4. Odds Ratios (OR) and Corresponding 95% CIs for Educational Attainment Among Individuals With Post-traumatic Stress Disorder (PTSD) Recorded Before the Corresponding Educational Milestone, Compared With Unaffected Individuals From the General Population (Stratified by Gender) and Compared With Their Unaffected Full Siblings, and Adjusted for All Psychiatric Disorders at the Same Time

eTable 5. Odds Ratios (OR) and Corresponding 95% CIs for Educational Attainment Among Males With Cognitive Ability Measures Available From Conscription Examination With Post-traumatic Stress Disorder (PTSD) Recorded Before the Corresponding Educational Milestone, Compared With Unaffected Individuals From the General Population