Cause-Specific Mortality and Physical Fitness in Mental Disorders

Epidemiological and Interventional Studies

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The sailor does not ask for tailwinds,

he learns to sail

G L

To Victor and Anton

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ABSTRACT

Mental illnesses are common and constitute a substantial health-related and financial burden on both the individual and society. Mental disorders in general have increased risk of somatic morbidity. An early age of onset is commonly seen in anxiety disorders and the prevalence of these disorders has increased in youth in recent years.

The overall aim of this thesis was to study mental disorders and the importance of cardiovascular fitness regarding both prevention and intervention and the association with cause-specific mortality. Studies I and II use data from several national registers to prospectively analyse if cardiovascular fitness in late adolescence is associated with future risk for mental disorder and how familial factors might impact the relationship. Furthermore, the aim in Study II was to estimate risk associated with specific causes of natural death in individuals with non-psychotic mental (NPM) disorders. Studies III-V emanate from a randomized, controlled clinical trial (RCT) set in primary care designed to evaluate the effects of an exercise intervention in persons with anxiety disorders. Patients were randomly assigned to either a) low-intensity training b) moderate to high intensity training or c) a control group, with three assessment points (baseline, post-intervention and one-year follow-up).

Study I and II were nationwide cohort studies of young men born between 1950 and 1987 who enlisted for military service between 1968 and 2005. Data was extracted from the Swedish Military Service Conscription Register. By linking conscription data to the Swedish National Hospital and Cause of Death Register we identified 1.1 million male conscripts in Study I and 1.8 million in Study II, with a follow-up of up to 46 years. We showed in Study I that lower fitness in late adolescent males was associated with increased risk of

schizophrenia and other psychotic disorders as well as anxiety and stress-related disorders in adulthood. Relationships persisted in models also adjusting for familial factors. In Study II we showed that young men diagnosed with NPM disorders had a long-term increased mortality risk, in particular due to gastrointestinal and infectious conditions with up to four-fold increased mortality risk for depressive and neurotic/adjustment disorders, personality disorders and alcohol-related/substance use disorders.

Study III is the study protocol describing our 12-week exercise intervention program for patients diagnosed with anxiety disorders within primary care. In Study IV, cross-sectional data at baseline from this RCT showed that severity of anxiety was associated with executive functions related to working memory but not with fluid intelligence. In Study V we could show that the 12-week exercise program improved symptoms of anxiety in patients with anxiety disorders in primary care, in both low and moderate- to high intensity exercise groups. No differences in effect sizes were found between intensity exercise groups.

In conclusion our findings show that low cardiovascular fitness in adolescence increases the risk for mental disorders later in life and that men with NPM disorders have an increased mortality risk. We could also show that a 12-week group exercise program proved to be an effective treatment for individuals with anxiety disorders in primary care. Further, we found an association between anxiety severity and working memory that need more elucidation. These findings, taken together with the knowledge that mental illness is increasing highlights the importance of preventive actions to improve cardiovascular fitness. Implementation of exercise in the treatment of anxiety disorders should be prioritized.

Keywords: Mental disorders; Anxiety disorders; Physical fitness; Exercise; Intervention Studies; Primary Health Care; Dose-response; Randomized Controlled Trial

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SAMMANFATTNING PÅ SVENSKA

Psykisk ohälsa är vanligt förekommande och bidrar till en betydande hälsorelaterad och ekonomisk börda både för individen och för samhället. Psykiatrisk sjukdom innebär en ökad risk för somatiska sjukdomar. Ångestsjukdomar debuterar ofta tidigt i livet och de senaste decennierna har vi sett en ökning av psykisk ohälsa bland unga. Det övergripande syftet med denna avhandling var att studera psykiatrisk sjukdom och betydelsen av fysisk kondition både gällande prevention och intervention och associationer med sjukdomsspecifik dödlighet. I Studie I och II används data från nationella register för prospektiva analyser av associationer mellan kardiovaskulär kondition i sena tonåren och framtida psykiatrisk sjukdom samt sjukdomsspecifik dödlighet hos individer med psykisk ohälsa i tonåren. Studie III-V utgår från en randomiserad klinisk studie med syftet att studera effekten av fysisk träning hos patienter med ångestsjukdom i primärvården. Patienterna delades in i låg-intensiv, medel-hög intensiv träning eller kontrollgrupp med uppföljning efter 12 veckor och 1 år. I både Studie I och II erhöll vi data från Värnpliktsregistret på unga män födda 1950-1987 som mönstrade mellan 1968-2005. Genom att länka samman dessa data med nationella patientregistret och dödsorsaksregistret så identifierade vi 1.1 miljoner respektive 1.8 miljoner män som vi kunde följa i upp till 46 år. I Studie I var kardiovaskulär kondition i ung ålder associerat med framtida riskökning för psykiatrisk sjukdom även efter justering för familjära faktorer. I Studie II sågs att unga män med psykiatrisk sjukdom hade en ökad dödlighet framför allt i mag-tarmsjukdom och infektioner med upp till fyrfaldigt ökad risk. Studie III är studie protokollet som beskriver vår randomiserade 12-veckors träningsstudie för patienter diagnosticerade med ångestsjukdom i primärvården. I Studie IV visade tvärsnittsdata från baseline att svårighetsgrad av ångestsymtom var associerat med nedsättning i exekutiva funktioner relaterade till arbetsminne men inte flytande intelligens. I Studie V kunde vi visa att ett 12-veckors träningsprogram gav en förbättring av ångestsymtom, både för låg- och måttlig-hög intensiv gruppträning. Effektmåtten mellan grupperna skilde sig inte åt. Sammanfattningsvis visar våra studier på att låg kardiovaskulär kondition hos unga män medför en ökad risk för psykiatrisk sjukdom senare i livet och att män med psykiatrisk sjukdom har en ökad risk för tidig död. Vi kunde också visa att ett 12-veckors gruppträningsprogram är en effektiv behandling för individer med ångestsjukdom i primärvården. Dessa fynd, tillsammans med kunskapen om att den psykisk ohälsan ökar, visar på betydelsen av preventiva åtgärder. Att förbättra den kardiovaskulära konditionen hos unga vuxna kan minska risken för psykiatrisk sjukdom och att använda fysisk träning som behandling för patienter med ångestsjukdomar borde vara prioriterat för samhället och sjukvården idag.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Nyberg J, **Henriksson M,** Åberg MAI, Rosengren A, Söderberg M, Åberg D, Kuhn HG, Waern M. Cardiovascular fitness in late adolescent males and later risk of serious non-affective mental disorders: a prospective, population-based study. *Psych Med. 2017; 28:1-10.* doi: 10.1017/S0033291717001763.

II. **Henriksson M,** Nyberg J, Schiöler L, Hensing G, Kuhn HG, Torén K, Löve J, Waern M, Åberg M. Cause-specific mortality in Swedish males diagnosed with non-psychotic mental disorders in late adolescence: a prospective population-based study. *J Epidemiol Community Health. 2018; Jul;72(7):582-588*. doi: 10.1136/jech-2018-210461.

III. Nyberg J, **Henriksson M,** Åberg D, Wall A, Eggertsen R, Westerlund M, Danielsson L, Kuhn HG, Waern M, Åberg M. Effects of exercise on symptoms of anxiety, cognitive ability and sick leave in patients with anxiety disorders in primary care: study protocol for PHYSBI, a randomized controlled trial. *BMC Psychiatry. 2019; Jun 10;19(1):172*. doi: 10.1186/s12888-019-2169-5.

IV. Nyberg J*, **Henriksson M*,** Wall A, Vestberg T, Westerlund M, Walser M, Eggertsen R, Danielsson L, Kuhn HG, Åberg D, Waern M, Åberg M. Executive function in Swedish primary care patients with anxiety disorder. *Equal contribution of these authors. *BMC Psychiatry 2021 Dec 9;21(1):617.* doi: 10.1186/s12888-021-03618-z.

V. **Henriksson M,** Nyberg J, Wall A, Westerlund M, Walser M, Eggertsen R, Danielsson L, Åberg D, Waern M, Åberg M. Effects of exercise on symptoms of anxiety in primary care patients: A randomized controlled trial. *J Affect Disord. 2022 Jan 15;297:26-34*. doi: 10.1016/j.jad.2021.10.006. Epub 2021 Oct 10.

Corrigendum to "Effects of exercise on symptoms of anxiety in primary care patients: A randomized controlled trial", published online ahead of print as J Affect Disord. 2021 Oct 10;297:26-34.

CONTENT

ABBREVIATIONS

BAI	Beck Anxiety Inventory
BDNF	Brain-derived neurotrophic factor
BMI	Body mass index
CBT	Cognitive behavioural therapy
CI	Confidence interval
D-KEFS	Delis-Kaplan Executive Function System
DALY´s	Disability adjusted life years
DSM-V	Diagnostic and Statistical Manual of Mental Disorders
EF	Executive function
EPN	The Regional Ethical Review Board
GAD	Generalized Anxiety Disorders
HAD	Hospital Anxiety and Depression scale
HR	Hazard ratio
ICD	International Classifications of Diseases
IQ	Intelligence Quotient
LISA	Longitudinal Integration Database for Health Insurance and Labor Market Studies
MADRS-S	Montgomery Åsberg Depression Rating Scale
MADRS-Sq2	Montgomery Åsberg Depression Rating Scale question 2
M.I.N.I	Mini International Neuropsychiatric Interview
NOS	Not Other Specified
NPM	Non-psychotic mental disorder
OCD	Obsessive Compulsive Disorder
PAR	Population attributable risk
PD	Panic Disorder
PIN	Personal identification number
PHYSBI	Physical Fitness and Brain - Interventional studies
PTSD	Post Traumatic Stress Disorder
RCT	Randomized Controlled Trial
SD	Standard deviation
WAIS-IV	Wechsler Adult Intelligence Scale IV
WHO	World Health Organization
VO_2 max	Maximum oxygen consumption
WM	Working memory

1 INTRODUCTION

Mental disorders including anxiety disorders are among the top 10 contributors to disability adjusted life years (DALYs) i.e. the composite of years lost due to premature mortality and years of healthy life lost due to disability. In particular adolescence and people of working age are affected [1] with early onset of symptoms and often chronic and lifelong diagnoses. They are globally widespread conditions with increased risk of cardiovascular disease [2, 3], premature death [4], decreased quality of life and daily functioning [5] and an increased risk of future marginalization [6], unemployment, sick leave [7] and suicide [8]. Suicide represents a significant cause of death with approximately 700 000 people dying by suicide globally every year and about 55 000 Europeans each year, of which three quarters are men.

According to findings from the World Health Organization (WHO) World Mental Health (WMH) surveys in year 2019, an estimated 15 %, equivalent to 137 million, of the general population in the European Region fulfill criteria for a mental disorder (combining depression, anxiety disorder, conduct disorder, substance use disorders, bipolar disorder, psychosis and schizophrenia) at some point in life [9] [10]. The overall global prevalence (in 47 countries) of anxiety disorders was estimated in year 2017 to be 11.4% but varies in different studies between 2.4 – 29.8 % [11].

Despite that many mental health conditions can be effectively treated at a relatively low cost today the gap is large between the need for treatment and its availability. In low- and middle-income countries, about 80% of those with mental disorders receive no treatment for their disorder [12]. Moreover, people with mental disorders often confront human rights violations, discrimination and stigma. In addition to support from health-care services, people with mental illness need social support and care.

Depressive disorder is the most common health problem in many EU states and one of the leading cause of disability globally. In Sweden, an increase in both incidence (the number of individuals who develop disease during a particular time period, new cases) and prevalence (the number of individuals in a population who have a disease at a specific period of time, total cases) of anxiety disorders have been reported in young men and women [13]. See figure 1. Lifetime prevalence for any anxiety disorder in Sweden is estimated to 25% [14].

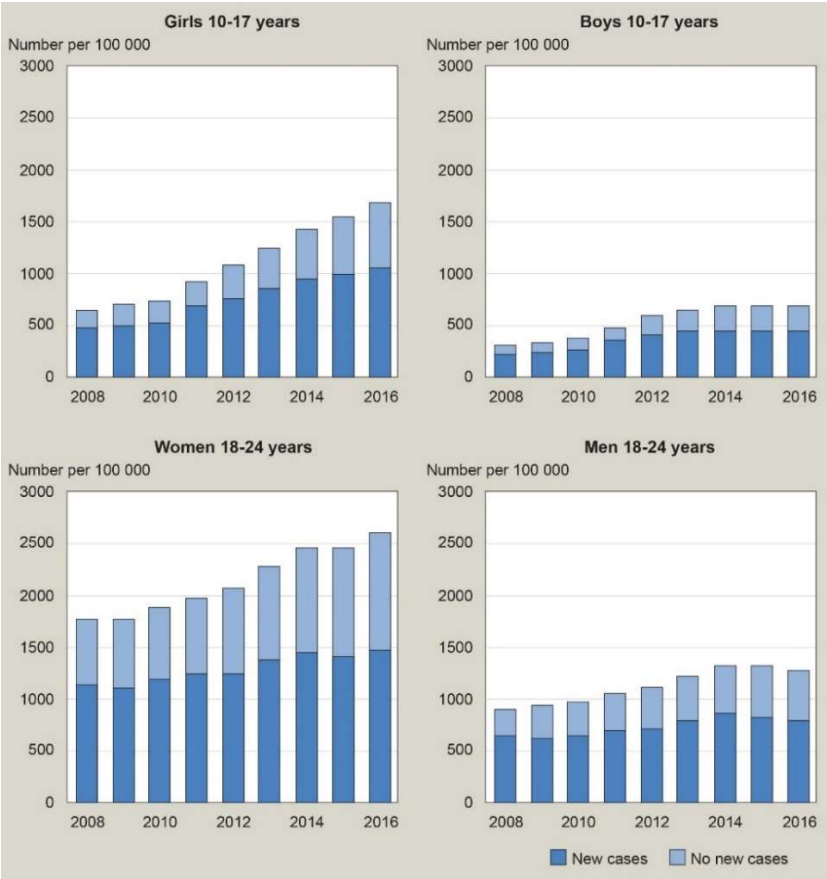

Figure 1. Prevalence (light blue bar) and incidence (dark blue bar) (number per 100 000) of children and young adults who had a hospital admission or specialist outpatient visit due to an anxiety disorder, during the period 2008–2016. At top, 10–17 years of age; at bottom, 18–24 years of age. Females are shown in the left panel, and males in the right panel. Reprinted and adjusted to English language with permission from the National Board of Health and Welfare [15], figure 4, page 24 (2021).

In 2020, 66 % of young women aged 16-29 reported symptoms of anxiety and worry; the corresponding figure in 2015 was 51 %. Among young men the numbers were 42 % in 2020 and 32 % in 2015 [15]. The prescriptions of antidepressants among young people, in particular women have increased, by 50% during a period of five years [15]. In addition to the rising prevalence of anxiety and depressive disorders, increasing numbers of young adults are diagnosed with psychiatric diagnoses such as bipolar disorders, substance use disorders and personality syndromes [13]. Figure 2 shows the increasing numbers of young adults having a specialist outpatient visit or a hospital admission due to a mental disorder between year 2006 to 2019 [15].

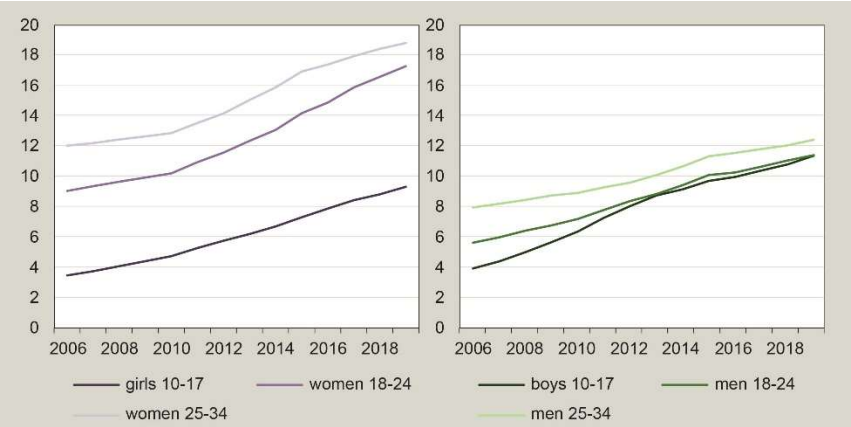

Figure 2. Prevalence (%) of children and young adults who had a hospital admission or specialist outpatient visit due to a mental disorder or who were picking up a prescription of psychotropic agents, during the period 2006–2019 for different age and gender. Reprinted and adjusted to English language with permission from the National Board of Health and Welfare [15], figure 4, page 24 (2021).

Mental illness is likely to continue to present a huge challenge for the society and young individuals growing up in Sweden in forthcoming years. In Sweden the majority of patients with anxiety and depressive disorders are managed in primary health care by a team of professionals (for example physiotherapist, psychologist, counselor therapist, occupational therapist and nurses) and their General Practitioners (GP's). The clinical implication is important as it has been estimated that 70% of patients seeking help for anxiety initially do so in primary care where costs for mental disorders are on the rise [15].

The present thesis aimed to add new knowledge about prevention, prognosis and treatment of mental disorders including anxiety disorders with both epidemiological and interventional approaches. Given the increasing occurrence of mental disorders in youths together with the elevated risk of somatic morbidity associated with mental illness, we need to know more about the long-term effects of adolescent mental disorders on mortality. For preventative measures, it is also important to investigate the effect of life-style factors such as cardiovascular fitness on risk of mental disorders including anxiety disorders [16].

There is strong evidence for physical exercise in treating depression [17, 18]. However, little research has focused on exercise in the treatment of anxiety and there is also a need to investigate the impact of different exercise intensities on anxiety symptoms. In Sweden there are guidelines from The National Board

of Health and welfare for treatment of depression with exercise, but guidelines for treatment of anxiety disorders are currently lacking.

Both cross-sectional, longitudinal cohort studies and intervention studies have shown that physical activity and improved cardiovascular fitness have a beneficial effect on cognitive processes, most convincingly executive functions in healthy individuals [19, 20]. As deficit in cognitive functions are reported in patients with anxiety disorders, including executive and working memory functions [16-18] exercise could have a potential to improve impairments in cognitive functions. Attentional problems, as being easily distracted and difficulties in focusing on ongoing tasks affect the working ability and the quality of life for patients with anxiety disorders [19].

All in all, mental disorders including anxiety disorders are common and increasing, co-morbidity of both somatic and psychiatric nature are frequent and patients also suffer from cognitive impairments and decreased daily functioning. The risk of premature death and the cost for the patients in quality of life and the economic burden for the society are high. If we can identify risk factors and find treatments easy to prescribe, with limited side-effects, this would increase the quality of life for these patients and lighten the economic burden for the community.

1.1 MENTAL DISORDERS

Definition - Mental health and common mental disorders

According to WHO there are many different mental illnesses, with various manifestations but generally distinguished by a combination of abnormal perceptions, emotions, thoughts and behaviour, as well as difficulties in social function. Individual attributes but also social factors, perinatal infections genetics, stress, nutrition, and exposure to environmental hazards include determinants of mental health and mental disorders. Historically, the concepts mental disorder and mental ill-health have evolved in different contexts and countries depending on cultural, social, political, economic, and environmental factors. Today it includes not only individual characteristics such as emotions, the ability to manage one's thoughts, and interactions with others but is more a continuum from the subjectively perceived feelings of discomfort of the individual to the more objective diagnosing of a state of illness by health care professionals. In the international scientific literature, the term Common Mental Disorder (CMD) is commonly used and includes depression and anxiety syndromes as well as Obsessive Compulsive Disorder (OCD) and Post-Traumatic Stress Disorder (PTSD).

To classify and diagnose diseases and causes of death in Sweden we use the ICD-system (International Statistical Classification of Diseases and Related Health Problems). Since year 1948, WHO is responsible for updating the classification. Today (since 1st January 2022) we use the ICD-11 that was approved by WHO at the 72nd World Health Assembly in 2019 [21]. In this thesis we use ICD 8, 9 and 10.

The American Psychiatric Association provides an official international manual for classifying and define diagnostic criteria for mental disorders, The Diagnostic and Statistical Manual of Mental Disorders (DSM) [22] which is used worldwide. The first version was published in 1952 and the latest revision, DSM-V, was published in 2013. In this thesis we use DSM-IV and V. DSM-V´s definition of mental disorder states:

“A mental disorder is a syndrome characterized by clinically significant disturbance in an individual's cognition, emotion regulation, or behavior that reflects a dysfunction in the psychological, biological, or development processes underlying mental functioning. Mental disorders are usually associated with significant distress or disability in social, occupational, or other important activities. An expectable or culturally approved response to a common stressor or loss, such as the death of a loved one, is not a mental disorder.” [23].

1.2 DEPRESSIVE AND ANXIETY DISORDERS

In Sweden, most patients, about 70 %, with anxiety and depressive disorders, are treated by their GP in primary health care, rather than by psychiatrists in specialist out-patient care. It is also in primary health care most antidepressants, approximately 65 %, are prescribed. Only 20 % of the patients are referred to specialists in psychiatry services [24]. Prescriptions of antidepressant medication among adolescents in Sweden are increasing, especially among females. Furthermore, females are more often treated with antidepressants compared to males in Sweden, see figure 3.

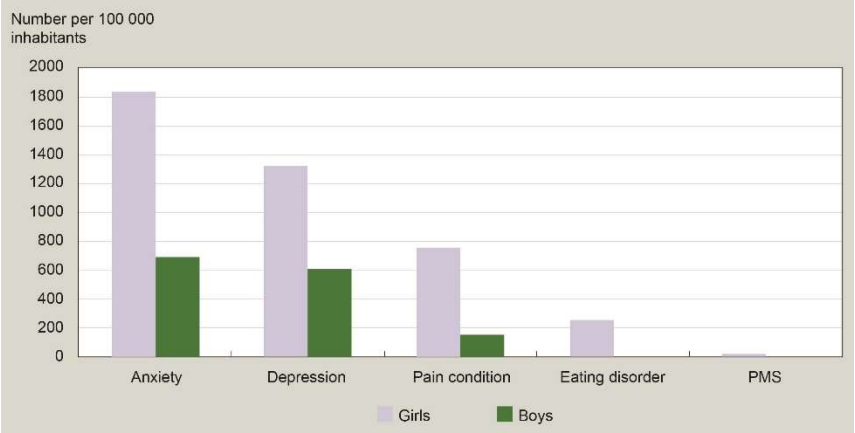

Figure 3. Diagnoses (numbers per 100 000) of young adults (10 to 24 years of age) diagnosed and treated with antidepressant medication in Sweden during year 2019. Light pink bars show females and green bars males. From left to right, anxiety, depression, pain condition, eating disorder and pre-menstrual syndrome (PMS). Reprinted and adjusted to English language with permission from the National Board of Health and Welfare [15], figure 1, page 6 (2021).

Depressive disorders

Depression is a CMD and one of the main reasons of disability worldwide. Globally, an estimated 264 million people are affected [24] and women are more affected than men. In Sweden it is estimated that lifetime prevalences for depression are approximately 36 % for women and 23 % for men [24]. Depression is characterized by sadness and depressed mood, loss of pleasure or interest in activities, pessimistic thoughts, feelings of guilt or low self-worth, disturbed sleep or appetite, tiredness, and poor concentration, sometimes accompanied with suicidal thoughts and/or thoughts about death for most of the day, nearly every day, for at least two weeks. It is often recurrent and usually last for 3-12 months, often even longer and substantially impairs

people's ability to function at work or school and to cope with daily life. Further, suicide could be a serious consequence of depression. Individuals with depression may also have multiple physical complaints with no apparent physical cause. Risk of recurrence is particularly high (60-70 %) among those with early onset [24].

Depression can be effectively treated with psychotherapy, such as cognitive-behavioural therapy (CBT) and/or antidepressant medication including selective serotonin reuptake inhibitors (SSRIs), selective noradrenalin reuptake inhibitors (SNRI) or tricyclic antidepressants (TCAs). In severe cases of depression (with suicidal thoughts or psychotic symptoms for example) treatment with electroconvulsive therapy (ECT), lithium or transcranial magnetic stimulation (rTMS) can be used. Treatment of depression ought to include psychosocial aspects to identify stress factors, such as economical problems, difficulties at work, physical or mental abuse and to strengthen sources of support from family and friends. Reactivating and maintaining social networks and activities is also important. The risk for recurrent episodes can decrease if treatment with antidepressant medication continues for at least 5-6 months after improvement of symptoms. In several cases it can be necessary with several years or even life-long preventive treatment. However, medication adherence is often poor, side-effects are common and waiting times for CBT are often long resulting in worse prognosis [25]. Prescribed physical exercise has been proposed as an effective alternative treatment for depression and in Sweden the National Board of Health and Welfare recommend it for mild to moderate depression [26, 27]. In contrast, there are no such recommendation for prescribed physical exercise in the treatment of anxiety disorders today.

Anxiety Disorders

Anxiety disorders are one of the most common mental disorders and are increasing in prevalence. Despite the disabling nature of anxiety, it is treatable. However, persons with anxiety disorders frequently remain unidentified and do not receive guideline-level care [12, 28]. Individuals may not seek professional help, may receive an incorrect diagnosis or present a broad range of clinical symptoms of anxiety that may be confused with somatic complaints, especially cardiac complaints, delaying treatment for between 9 and 23 years [12].

Symptoms of anxiety range from feelings of unpleasantness and worry to a state of anxious arousal referring to the somatic symptoms of anxiety frequently found in Panic Disorder (PD) including flushed skin, shortness of breath, tremors, and sweating, pulse and blood pressure increase and pupil dilation. These symptoms known as the "fight-or-flight" system or "threat

circuit" are caused by increased sympathetic activation of the autonomic nervous system (ANS). Individuals with Generalized Anxiety Disorders (GAD) experience more of a constant worry and anxiety in several aspects and situations in their daily lives and often have difficulties in coping and control their anxiety which can lead to catastrophic thinking. Other symptoms are muscle tensions, pains and sleeping disturbances that often can be misinterpreted for other somatic disorders.

Furthermore, anxiety disorders are believed to be polygenic, with genetic heritability estimates of between 30% to 50%. Environmental factors such as childhood abuse and neglect or fearful and stressful life events have been related to increased risk of anxiety disorders later in life [28]. Most anxiety disorders have their onset in childhood and females have twice as high risk of developing an anxiety disorder compared to males. The lifetime prevalence of PD worldwide has been estimated to 2% to 5% and 3% to 5% for GAD. Comorbidity of psychiatric and somatic nature is common for both PD and GAD. Adolescents with anxiety syndromes are at high risk of relapse in adulthood.

DSM V´s definition of PD follows four diagnostic criteria:

- Repeated unexpected panic attacks that characterize as a short intense fear or discomfort that reaches a peak within minutes, when a number of cognitive and somatic symptoms of anxiety occur (at least four)
- At least one or more attacks followed by 1 month (or more) of fear of another panic attack and their consequences (e.g. losing control) and/or significant maladaptive behavior related to the attacks (e.g. avoidance)
- It is not attributable to the physiologic effects of any substance use or another medical condition
- The disturbance is not better described by another mental disorder

DSM V´s definition of GAD follows six diagnostic criteria:

- Excessive worry/anxiety occurring more days than not for leastwise 6 months
- The individual finds it difficult to control the anxiety
- The anxiety and are associated with at least three of the following six symptoms: restlessness, being easily fatigue, difficulty concentrating, sleep disturbance, irritability, muscle tension

- The worry, anxiety or physical symptoms cause clinically significant distress or impairment in occupational, social, or other important areas of functioning
- It is not attributable to the physiologic effects of any substance use or another medical condition
- The disturbance is not better described by another mental disorder

Standard treatment in Sweden for anxiety including GAD and PD is antidepressant medication where first line is serotonin reuptake inhibitors (SSRI). Second line treatments are serotonin and noradrenerg reuptake inhibitors (SNRI) or tricyclic antidepressants, but these are often accompanied with more side-effects. An alternative and/or complement to medication is CBT. For PD, CBT is also used as first line treatment.

Diagnosing depressive and anxiety disorders

The Swedish National Board of Health and Welfare state diagnostic and treatment guidelines for depressive and anxiety disorders [21]. The latest version was updated in 2020, where the diagnostic process differs from earlier forms. It is now recommended to use the interview Mini international neuropsychiatric interview (MINI) and Clinical interview for DSM-IV axis I disorders, clinical version (SCID-I) after the standard clinical assessment of both depressive and anxiety disorders. In both primary health care and specialist out-patient health care it is believed that only 50% of those with depressive and anxiety disorders are diagnosed and these interviews are thought to be a tool to improve the diagnostic process, primarily in psychiatric specialist care. In primary care it is more common to use the Montgomery Åsberg Depression Rating Scale (MADRS-S), Beck Anxiety Inventory (BAI) or the Hospital Anxiety and Depression scale (HAD) when diagnosing depression and anxiety. Depressive disorders are subdivided into mild, moderate and severe depression. In Sweden, when classifying and diagnosing depression according to ICD-10, clinicians use, together with a clinical examination, MADRS-S [22] a self-assessment scale with maximum 54 points. It is divided in 9 questions (symptoms of depression as above) and ratings are categorized in no/minimal depression (score 0–12), mild (score 13–19), moderate (score 20–34) and severe (35 or more). For primary care clinicians diagnosing anxiety, BAI is clinically a well-established anxiety self-assessment scale [29]. BAI primarily evaluates somatic symptoms (respiratory distress, experience of palpitations, tremor, sweating etc.) and was created to be relatively clean from depressive content [29]. It is organized in 21 items,

with scoring from nothing (0 p), slightly (1 p), moderately (2p) and severely (3p) and total ratings range from nothing, minimal/mild (score 0–15), moderately (score 16–25) and severely (score 26–63). Both reliability [30] and validity [31] are reported to be high. HAD consists of 14 questions where 7 of them concerns anxiety symptoms and 7 depression symptoms. An alternative for diagnosing PD is the symptom assessment scale The Panic Disorder Severity Scale - Self Report (PDSS-SR) with 7 questions characterizing panic attacks and diagnostic criterium.

1.3 BIPOLAR AND PSYCHOTIC DISORDERS

Diagnosing mental disorders should always be considered if there is an individual suffering and/or loss of function. In more severe psychiatric disorders, the perception of reality can also be impaired, as in psychotic disorders like schizophrenia.

Bipolar disorder

Bipolar disorder affects about 45 million people worldwide and is equally common in women and men. Life-time prevalence is estimated to 1-2 % [14]. The influence of genetic factors is high, ranging from 70 to 90 % [32] in bipolar disorders [33]. According to the DSM-V classification bipolar disorders are divided in three categories: bipolar I, bipolar II and cyclothymic disorders.

Bipolar I disorder is defined by the presence of at least one manic episode and 80 to 90% of those also have depressive episodes. The manic episodes are characterized with a range of manifestations, including decreased need for sleep, over-activity, elevated or irritable mood, over-activity, rapid speech and inflated self-esteem. Psychotic symptoms such as delusions and hallucinations also occur in up to 75% of the manic episodes.

Bipolar II disorder is characterized by episodes of depression, alternating with hypomania. Hypomania is characterized by manic symptoms that do not affect the patient's daily functioning; there are no psychotic symptoms.

Cyclothymic disorder is characterized by milder recurring depressive and hypomanic states, lasting for at least 2 years.

Effective treatments, including mood-stabilizers, are available for treating the acute phase of bipolar disorder and for preventing relapses. Psychosocial support is also an important component of the treatment. It is important to receive adequate treatment as soon as possible and continue to get long-term prophylactic medication since recurrent episodes are common.

Schizophrenia and other psychoses

Schizophrenia is a burdensome mental disorder, affecting 20 million people worldwide according to WHO. Furthermore, it is the most severe mental disorder in aspects of disease burden, comparable to terminal cancer and have 2.5 higher mortality risk compared to the general population [34]. The incidence in Sweden is estimated to 15 individuals per 100 000 habitants and the prevalence to approximately 4.5 in a population of 1 000 individuals. The loss of functions for persons with schizophrenia are severe, leading to unemployment for 80-90 % of the affected [35]. In Sweden, it is estimated that 30 000 – 40 000 people are affected and in need for support from the society due to schizophrenia and other psychotic disorders.

Schizophrenia, including psychotic disorders, are represented by distortions in perception, emotions, thinking, language, sense of self and behaviour. Common psychotic symptoms are delusions (fixed false beliefs or suspicions, even when there is evidence of the contrary) and hallucinations (hearing, seeing or feeling things that are not there). The criteria for schizophrenia according to DSM-V includes two or more symptoms of following:

- Negative symptoms i.e avolition and diminished expression
- Severely disorganized or catatonic behavior
- Disorganized speech
- Disorganized behaviour
- Hallucinations
- Delusions

Together with a substantial social and occupational dysfunction (during at least 6 months) the symptoms must persist for at least one-month period (for DSM-V criteria the clinical symptoms must persist for at least 6 months).

Schizophrenia usually debuts in late adolescence or early adulthood. For males the debut occurs between 15 -25 years of age and for women at 25 - 35 years. Males also have more negative symptoms (such as diminished emotional expression or avolition) and worse prognosis. At age 20, 20-40% of the affected have experienced their first symptoms. The etiology of schizophrenia is multi-factorial including heredity and psycho-social stress.

Treatment includes both anti-psychotic medication and psychosocial support. Today's anti-psychotics primarily work by blocking or binding to the dopamine D2 receptor. New treatments affecting other pathways such as glutamate are in progress.

1.4 PHYSICAL ACTIVITY AND MENTAL HEALTH

Physical activity has many health benefits and is associated with a lower risk of many chronic diseases [36-38]. We also know today that a sedentary lifestyle is associated with an elevated risk of illness. Replacing sedentary time with physical activity of any intensity provides health benefits. The Swedish recommendations for physical activity are the same as the recommendations of the WHO, which says that all adults should be physically active for a minimum of 150 minutes per week of at least moderate intensity in total. WHO's recommendations for adults also state that muscle-strengthening activities in more than two days a week and limiting the amount of time spent being sedentary provides health benefits.

Several models have been suggested to explain the positive effects of regular exercise on mental disorders. Psychological theories propose that mental distraction and improved self-confidence can be a part of the improvement. On multiple levels of evidence (such as molecular, cellular, blood, CNS, clinical and epidemiological level) a chronic low-grade inflammation and increased levels of pro-inflammatory cytokines has consistently been described in patients with mood disorders [39]. A boost in cell proliferation and cell survival in the hippocampus, which can occur at many stages of development during adolescence and older age, is one of the most consistently observed effects of exercise treatment [40].

The proliferation of new cells in the brain increases the requisite for nutrients. This stimulates the growth of new blood vessel in the hippocampus and subventricular zone (SVZ). The presence of polypeptides such as insulin-like growth factor 1 (IGF1) and vascular endothelial growth factor (VEGF) is thought to be required for angiogenesis [41]. In young rodents, aerobic exercise increases the production and release of both VEGF and IGF1, leading to the formation of new blood vessels. Together with VEGF and IGF1, brain-derived neurotrophic factor (BDNF) is another protein that is upregulated by physical exercise. Hippocampal BDNF levels have been directly associated with memory processes observed in rodents that are treated with exercise. BDNF also regulate the extracellular signal-regulated kinase (ERK), which has a central part in the pathogenesis, symptomatology, and treatment of depressive disorders through pathways in the prefrontal cortex and the hippocampus [42].

Aerobic or resistance training enhances circulating levels of IGF-1 and the expression of for example irisin pathway which stimulates the expression of PI3K, which inhibit inflammatory mechanisms. Furthermore, the glycogen synthase kinase 3 beta (GSK3β) is inhibited by the irisin activation [40]. See figure 4.

Taken together, the findings put forward that physical activity is advantageous across the human lifespan, but it is unclear whether there is a dose-response relationship between cardiovascular fitness and effects on the brain.

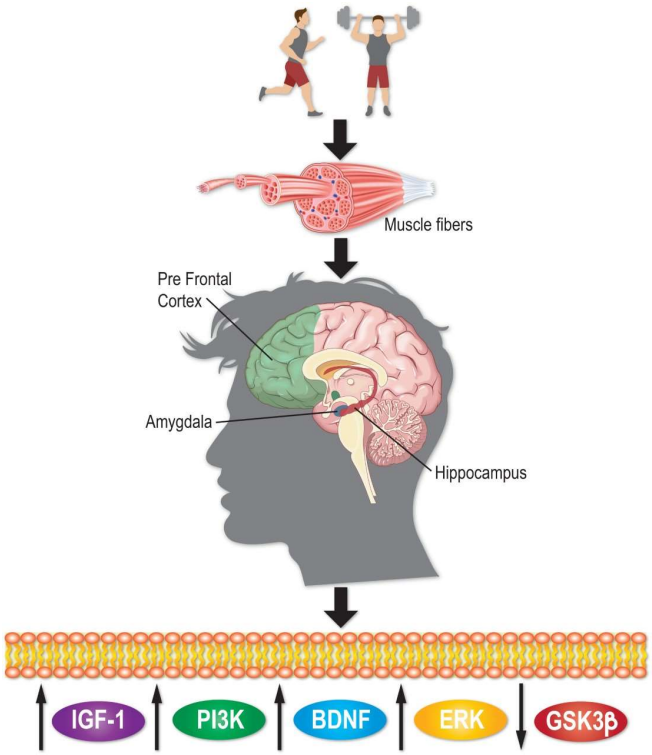

Figure 4. Aerobic and resistance physical exercise regulates the expression of proteins and have beneficial effects on mental health enhancing IGF-1, P13K, BDNF (serum and brain), ERK, and reducing GSK3(beta) levels. Published with permission from Jenny Nyberg, 2021.

1.5 REGISTER BASED RESEARCH

All registered residents in Sweden have a unique ten-digit personal identity number (PIN), which they receive from the Swedish Tax Agency at birth or immigration. The PIN was introduced in 1947 [43] and states the date of birth by six numbers and four additional numbers that also states the sex of the individual. The third number of the additional four, will be odd number if your legal sex is male, but even if your legal sex is female. The last number is a control number. It is used unchanged throughout the individuals life and used as a personal identifier [44]. The PIN is extensively managed in providing information to other authorities and in public administration such as contacts with health care providers, education, migration, passport administration, in commercial and financial bank situations as well as in medical research. The PIN is utilized as a linkage tool between registers and to keep record of individuals emigration and reimmigration. By almost complete coverage of the population, it has enabled formation of various high-quality national registers kept by the Swedish state at the National Board of Health and Welfare and at Statistics Sweden.

Population-based cohort studies

In Sweden we have a unique possibility to study both male and female risk factors for specific outcomes using our nationwide structure for documentation in registers throughout life. These registers give researchers the opportunity to study different questions for defined populations and the results should be generalizable to the whole population addressed in the study hypothesis. There are three types of observational studies: cross-sectional surveys, case–control studies and cohort studies. Observational studies do not determine which specific subject gets exposed to a risk or given a new treatment. This contrasts with the randomized controlled trial, where the researcher randomly allocate exposures to subjects. Studies relating exposure to outcomes and investigating the etiological factors are often observational; the researcher simply observes what happens. The chosen group of persons, the “cohort” for example born during a particular year is then followed over a period of time regarding outcomes. In a cohort study the researcher can identify the persons that have been or will be exposed to a risk factor that could increase the possibility of occurrence of disease or other events. An association between an exposure and an outcome may also both strongly associate with a third variable, a so-called confounding factor. In observational studies, it is important to consider potential confounding when performing the statistical analyses. If not, the results may be distorted and show a cause-and-effect relationship that does not actually exist [45].

Two of the studies in this thesis (Studies I and II) are prospective, population-based cohort studies.

Figure 5. Overview of reporting research and science with different study design, from laboratory and animal research to meta-analysis. Printed with permission from author Jenny Nyberg, 2021.

1.6 RANDOMIZED CLINICAL TRIAL (RCT)

The RCT is defined as a prospective study and is used to investigate the relative efficacy of treatments or interventions in humans. Usually, one (or more) new treatment or intervention is compared against a standard treatment or no treatment (control). A parallel design implies that the included participants are randomized to one or more study arms and each study arm will be allocated a different intervention or a control group. After randomization each participant will stay in their assigned treatment or control arm for the duration of the intervention. The RCT is considered to have a central role in the development of new therapies but is also used in for example evaluation of screening procedures and other medical problems.

Randomization was introduced by the founder of modern statistics, RA Fisher (1890–1962) and developed in medicine by Austin Bradford Hill (1897–1991) [45]. At first, randomization was regarded as a harmful method to allocate a treatment to an ill person. It was later justified and considered the only fair method to decide who got treated and who did not in a time when treatment was expensive and restricted. Nowadays it is viewed as the only way to ensure absence of allocation bias during the allocation process. Allocation bias is a bias arising from a systematic difference in assigning participants to the treatment groups.

Inclusion and exclusion criteria for entering the study are defined in the study protocol. Potential participants are assessed for eligibility. If the person fulfilled the criteria for inclusion and did not meet the exclusion criteria, the person is randomized.

By randomizing we ensure that the assignment of an individual to a certain group or treatment is decided by chance, and not predicted in advance. This could be obtained through the draw of a card, the toss of a coin, or as more often used today a computer-generated random number. The investigator will not influence who gets which treatment or intervention. This ensures that, in a large population, the participants are equally represented in each treatment/intervention/control arm and that the probabilities obtained from statistical tests are valid.

Blind assessment is the desirable way of conducting a trial and gives the study high validity. The maximum degree of 'blindness' is "double-blinded" in which neither the patients nor the physicians are aware of the randomized treatment group.

To improve the reporting and conducting of RCT's the CONSORT (Consolidated Standards of Reporting Trials) statement was developed in 1996. The 2010 version includes 25 items which should be covered in any trial report as well as a suggested flow chart to describe the progress through the

trial. It is evidence-based but does not provide recommendations for designing, conducting, and analysing trials [46]. It offers a standard method for authors to prepare reports of trials and to provide enough information for readers to know how the trial was performed and to be able to judge whether the findings are likely to be reliable.

When multiple scientific studies addressing the same question exist, for example many RCT's conducted are small, replicated and in some cases not published and where each individual study reports measurements expected to have some degree of error, a meta-analysis may be performed. In a meta-analysis, results of several scientific studies are combined and statistical analyses performed in order to determine overall trends. A systematic review on the other hand, attempts to gather all available empirical research on a specific question and by using systematic and clearly defined methods obtain answers for that question. See figure 5 for an overview of different study designs.

The Cochrane is a global independent network of professionals and a non-profit organization from 220 countries working together to produce reliable, accessible information about health research, free from conflicts of interest and commercial sponsorship. They are producing reviews published online in the Cochrane Library, summarizing the best-founded evidence generated through medical and health research to use in decisions about health.

In the present thesis we present the Study protocol (Study III) and results (Studies IV-V) from the RCT called PHYSBI (Physical Fitness and Brain-Interventional Study).

1.7 KNOWLEDGE GAPS

Mental disorders are one of the globally largest healthcare challenges of this century. Prevention strategies are needed, and one modifiable risk factor is cardiovascular fitness. Low cardiovascular fitness in late adolescence is not only associated with increased risk of serious depression and bipolar disorder in adulthood [33] but also a strong predictor of all-cause mortality and cardiovascular disease, also after adjusting for physical activity [47]. There is a knowledge gap regarding the relationship of cardiovascular fitness and future risk of other mental disorders such as psychotic disorders and neurotic, stress-related and somatoform disorders, that is non-affective mental disorders. Further, familial influences and the role of premorbid fitness needs to be elucidated.

It is well known that mortality risk is increased among individuals with psychotic illness, but also NPM disorders are associated with premature death [4, 48]. Given the fact that the younger population with mental disorder have higher mortality risk it is important to investigate the long-term cause-specific mortality among late adolescents with NPM disorder. Only a few studies, with short follow-up times and lacking data on cause-specific mortality, provides risk estimates for premature death for this group.

Patients with anxiety disorders often express a subjective experience of deficit in cognitive performance. Research in this field is sparse and often inconsistent and heterogeneous [49-51]. Some evidence point at impairments in executive function (EF) and especially in the association between anxiety disorders and cognitive function [52]. Evidence whether level of EF is associated cross-sectionally with severity of anxiety symptoms in patients diagnosed with anxiety disorders in a primary care setting, is lacking.

Low cardiovascular fitness in late adolescent males is found to be associated with increased risk for mental disorders in adulthood. While there is convincing evidence from RCTs that test exercise interventions in the prevention and treatment of depression, high quality research on such interventions for persons with anxiety disorders is rather sparse. Several of the interventions included in a meta-analysis were at high risk of bias due to low power and small sample sizes, short follow-up time and not well-controlled trials [36, 53]. Furthermore, research on anxiety disorders with different types and dosages of exercise are uncommon and interventional studies have rarely been conclusive [54-56]. Only one meta-analysis compared high-intensity exercise with low-intensity showing superiority for high-intensity exercise [57]. A focus on long-term follow-up and well-controlled and powered studies are needed.

2 AIMS

The overall aim of this thesis was to study mental disorders and the association with cause-specific mortality and the importance of cardiovascular fitness both regarding prevention and intervention. The epidemiological part included usage of several national registers to prospectively analyse cause-specific mortality risk associated with mental illness, as well as associations of cardiovascular fitness and future mental disorders. The interventional part was an RCT aimed at studying the effects of an exercise intervention during 12 weeks on symptoms of anxiety in primary care patients with anxiety disorders. An additional aim was to analyse cross-sectional associations between anxiety severity and cognitive functions in the RCT population.

The specific aims of the individual studies were:

I. To study if cardiovascular fitness in late adolescence is associated with future risk of serious non-affective mental disorder and how familial factors may influence such a relationship.
II. To study specific causes of natural death in late adolescent men with NPM disorders.
III. To finalise and publish the study protocol for PHYSBI, an RCT aimed at studying the effects of exercise on symptoms of anxiety and cognitive ability in patients with anxiety disorders in primary health care.
IV. To study cross-sectional associations between cognitive performance, with focus on executive function, and anxiety severity in primary care patients diagnosed with anxiety disorders.
V. To determine whether a 12-week group exercise intervention, with different intensities, could decrease anxiety symptoms compared to a control group in patients diagnosed with anxiety disorders in primary care.

3 PATIENTS AND METHODS

This thesis is based on five studies, one of which (Study III) is the published protocol for Study V and does therefore not include any analyses. The study designs and methodologies are summarized in Table 1, and statistical methods are detailed in Table 5.

Table 1. *Study designs (Study I – II and IV - V).*

	Study I	Study II	Study IV	Study V
Study design	Prospective cohort	Prospective cohort	Cross-sectional	RCT
Setting	Swedish Military Service Conscription Register	Swedish Military Service Conscription Register	PHYSBI - patients recruited from primary care in Region Västra Götaland and Region Halland	PHYSBI - patients recruited from primary care in Region Västra Götaland and Region Halland
Inclusion Criteria	Male conscripts, no mental illness	Male conscripts with and without NPM disorders	Anxiety disorder (M.I.N.I) Both genders Ages 18-65	Anxiety disorder (M.I.N.I) Both genders Ages 18-65
Number of participants	1 109 786	1 784 626	189	153
Years of inclusion	1968–2005	1968–2005	2017-2019	2017-2020
Years of follow-up	1971-2010	1968-2014	NA*	2017-2021
Exposure	Cardiovascular fitness (objectively measured)	NPM disorders	Severity of anxiety (BAI) Cognitive function (WAIS-IV and D-KEFS Design Fluency subtest)	12-week cardiorespiratory /resistance exercise 3 times/week (one hour/times) with low or moderate to high intensity or control group
Study outcome	Serious non-affective mental disorders	Cause of death	Association between severity of anxiety and cognitive functioning	Improvement in anxiety symptoms (BAI, MADRS-S and MADRS-S question 2)
Outcome assessment	Swedish National Hospital Register	The Swedish Cause of Death Register	BAI. Cognitive function (WAIS-IV and D-KEFS Design) Fluency subtest)	12-weeks follow-up assessment (BAI, MADRS, VO2max, and muscle strength)

*NA (not applicable)

3.1 METHODS (STUDY I AND II)

The study cohorts in the epidemiological Studies I and II were derived from the Military Service Conscription Register and "Pliktverket" (in Swedish), which are based on enlisting Swedish males. Conscription register data were linked to several other registers and then coded and anonymised by Statistics Sweden.

Other registers used in this thesis follows below.

3.1.1 NATIONAL POPULATION REGISTERS

The registers utilised in Studies I and II are the Swedish Military Service Conscription Register, the Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA), the National Patient Register, the Multi-Generation Register and the Cause of Death Register. Information on emigration and parental education was taken from LISA and date of death was obtained from the Swedish Cause of Death Register.

The Military Service Conscription register

Data was extracted from the Swedish Military Service Conscription Register, established in 1952, with digitisation of data from 1968 and considered complete from 1969. During this period, until the elimination of the mandatory military service in 2010, all Swedish males within the age range 18-24 years had to enlist according to Swedish law. Exceptions and exemptions from enlistment were made only for men in prison or those with severe medical conditions or functional disabilities (limited to 2% to 3% per year).

Compulsory military service for all Swedish 18-year-old men was introduced in 1901. About 30,000 men per year started their military education up to the 1950s. After the two World Wars, the numbers rised to 50,000 men annually. Uppsala Swedish Air Force was in 1980 the first to offer military training for women, but it was not until 2010 that conscription became voluntary and at the same time gender neutral. In 2018, after the use of registers in this thesis, the Government of Sweden decided, with intention to maintain military readiness, that conscription-based recruitment had to be reintroduced. Today approximately 16 000 18-year-olds of both sexes are recruited annually [58]. In 2020, 5 500 men and women started their military training.

At enlistment, physicians and psychologists at any of nine conscription centers examined the men during a couple of days (1-3) according to a standardised procedure. In addition to recording medical conditions, measurements of height, weight, blood pressure, cognitive performance, cardiovascular fitness, and stress resilience were taken. A psychologist evaluated psychiatric symptoms, for example the NPM disorders in study II, during a structured interview. Conscripts with such symptoms were referred to a physician, and psychiatric disorders were assigned according to the ICD. The limit for referral to a psychiatrist was low in order to ensure that men with psychiatric conditions did not participate in the following military training [59]. Cardiovascular fitness was assessed using a maximal ergometric cycle test (Wmax/kg) as described in Study design [60].

The Cause of Death Register

A death in a Swedish resident is certified by a physician in two steps. First, the physician confirming the death immediately reports the death, by a "notification of death" (dödsbevis in Swedish) to the Swedish Tax Agency. This is a legal obligation which must be completed before a funeral can take place. Secondly, the medical death certificate (dödsorsaksintyg in Swedish) which includes the cause of death must be sent to the National Board of Health and Welfare within 3 weeks. If the cause of death is unclear, an autopsy is performed. The cause of death is then classified according to the ICD. The Cause of Death Register is available electronically since 1952 for register-based research and covers almost all deaths since 1961. The register is updated every year and is considered to have high validity [61].

The Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA)

LISA has been available and administered by Statistics of Sweden since 1990. It contains information from several national registers about labour market, unemployment, socio-economic factors and educational data. With this database it is possible to integrate individual information for register-based research. LISA has a national coverage of 80% and is updated annually since 2001 for Swedish residents 16 years or older [62]. For Studies I and II we used information about parental educational level for conscripts, as an indicator of socioeconomic status.

The Multi-Generation Register

This register is a part of the Total Population Register in Sweden; information comes from the National Tax Board. Since 1961 it covers all Swedish residents born in 1932 or later who have been registered residents in Sweden. These persons are called index persons. The register contains links between the about 11 million index persons and their biological parents. Connecting information from Statistics Sweden, Register of Birth and the Total Population Register (TPR) makes it possible to include persons persons who were born or immigrated during a given year. With this register it is also possible to identify biological parents, full or half siblings, children and cousins of an index person. The information is used for various types of research including medical studies and register-based research [63]. In the present thesis it is utilized in Study I to identify full brothers in the models that examined the relationships with illnesses in brothers. In Study I and II parental education were used as covariates in models that examined potential impact of parental education on the association between NPM disorders and cause-specific mortality in adulthood.

The Swedish National Hospital register

It is obligatory for all hospitals in Sweden, publicly and private funded, to register one primary diagnosis (according to the ICD) in the Swedish National Hospital Discharge Register. At outpatient visits or upon discharge from the hospital, patients receive one principal diagnosis. This register is also called The Swedish National Inpatient Register (IPR) and is a part of The National Patient Register. It was founded in 1964 under the name The Swedish National Patient Register [64]. Register coverage for inpatient care increased gradually during 1968–1986. It is considered complete for all public and specialist inpatient care since 1987. Specialist outpatient visits, including psychiatric care, have been registered since 2001 [64]. Validation of the register has been conducted in several studies, a review in 2011 showed a high positive predictive value of generally 85-95% but differ between diagnoses [65].

3.1.2 STUDY DESIGN STUDY I

In Study I, in order to examine the impact of cardiovascular fitness and later risk of serious non-affective mental disorders, we performed a prospective population-based cohort study. We included all Swedish men (n=1 109 786) who underwent conscription examinations, between 1968 and 2005. They were followed for 3–42 years, between 1971 and 2010. We linked data from the conscription register to LISA, the Multi-Generation Register, the Swedish National Hospital Register and the Swedish Cause of Death Register.

We excluded men with prior or ongoing psychiatric disorder identified in the Swedish Military Service Conscription Register and/or the Swedish National Hospital Register (n = 56 343). Men lacking complete information from the military conscription as well as men with outcome diagnoses registered during the first 3 years after conscription were also excluded resulting in a final study cohort of 1 109 786 men. Three different ICDs was used during the follow-up: 1968–1986 (ICD-8), 1987–1996 (ICD-9) and 1997 onwards (ICD-10).

Cardiovascular fitness test at conscription

The exposure, cardiovascular fitness, was measured at conscription using a standardized procedure. Using a bicycle ergometer measuring work rate divided by body weight (Wmax/kg), result was transformed into scores, with 1 as the lowest and 9 as the maximal performance. The test has been shown to have good reliability and validity [60, 66]. For further description of the test see Article I.

Confounders Study I

The Multi-generation register was utilised in Study I to identify full brothers in the models that examined the relationships with illnesses in brothers. We obtained data from the Swedish Military Service Conscription Register for measures of region, year for enlistment, cognitive performance (IQ) and body mass index (BMI) as confounders. Information on mother's and father's education level was collected from the LISA database (80% coverage) and were graded in six levels.

To reduce possible effects of variation in diagnosis rate and differences in conscription procedures depending on conscription year, we adjusted for calendar year by stratifying by decade. Conscription test center was considered a possible confounder since the men enlisted in nine different regional test centers and differences among regions and test centers could introduce bias. Another potential confounder is BMI since it is positively associated with anxiety disorders in adults [67] and was therefore adjusted for.

Table 2. *Outcome diagnostic categories (non-affective mental disorders), frequencies (with 3 years latency from conscription date) and ICD codes, of male conscripts in the National Hospital Register, Study I.*

Diagnostic category	ICD-8	ICD-9	ICD-10
Schizophrenia and schizophrenia-like disorders (n = 4641)	295	295	F20, F25
Other psychotic disorders (n = 5564)	297, 298.2, 298.3, 298.9, 299.9	297, 298C, 298E, 298W, 298X	F22, F24, F28, F29
Neurotic, stress-related and somatoform disorders (n = 17 262)			
Phobic anxiety disorders (n = 611)	300.2	300C	F40
Other anxiety disorders (n = 6034)	300.0	300A	F41
Obsessive–compulsive disorders (n = 513)	300.3	300D	F42
Reaction to severe stress and adjustment disorders (n = 8672)	307	308, 309	F43
Somatoform and dissociative (conversion) disorders (n = 1349)	300.1, 300.7, 305	300B, 300H, 306	F44, F45
Other neurotic disorders (n = 941)	300.5, 300.6, 300.8, 300.9	300F, 300G, 300W, 300X	F48

Outcome assessments during the follow-up period

The outcome assessments studied were diagnostic codes from the Swedish National Hospital Register identified according to the ICD. Non-affective mental disorders were divided into following subgroups: (a) schizophrenia and schizophrenia-like disorders, (b) other psychotic disorders and (c) neurotic, stress-related and somatoform disorders. For ICD codes see Table 2.

To diminish the risk of possible reverse causation the analyses were restricted to men with first-time diagnoses recorded 3 or more years after conscription. Follow-up period lasted from January 1971 to December 2010 and an individual could be included in more than one diagnostic group.

Statistical method Study I

To evaluate the influence of cardiovascular fitness in mentally healthy male conscripts on the first occurrence of non-affective mental disorders, as described in Table 2, we used Cox proportional hazards models. Subjects were censored at time of (1) first onset of outcome diagnosis, (2) death, (3) emigration, or (4) at the end of follow-up. To measure potential effects of genetic factors, sub-analyses were performed within full brother pairs and therefore many of the early childhood risk factors could be accounted for, including genetic makeup and shared environment.

3.1.3 STUDY DESIGN STUDY II

As in Study I this is a prospective cohort study including all Swedish men (n=1 784 626) who underwent conscription examinations at age 16 to 25 between 1968 and 2005. At or prior to conscription 74 525 men were diagnosed with NPM disorders. They were followed over a period of up to 46 years, between 1968 and 2014. Median follow-up time was 26 years.

To investigate if young men with NPM disorders had a long-term increased cause-specific mortality risk, cases of men with NPM disorders prior to or at baseline (conscription) were compared with the population of men without NPM disorders at baseline. All conscripts were examined by a physician and psychiatric disorders were identified according to ICD 8, 9 and 10. In this study, NPM disorders were divided into three subgroups; (a) depressive and neurotic/adjustment disorders, (b) personality disorders and (c) alcohol-related and other substance use disorders. For ICD codes see Table 3.

To prevent incorrect classification of young men with prodromal episodes of severe mental disorders, all men with hospital admissions for and/or diagnosed with non-affective psychotic disorders and bipolar disorder (irrespective of time of onset) were excluded.

Information on emigration and parental education were taken from the LISA register. Date of death was obtained from the Swedish Cause of Death Register.

Confounders Study II

To obtain data for confounding we used the same registers as in Study I. Test centres could result in bias and was adjusted for. Since early obesity [68] and hypertension [3, 69] are risk factors for premature death, adjustments for BMI and systolic and diastolic blood pressures were performed. Moreover, parental education [70], cardiovascular fitness [33] and IQ [71] may influence the association between NPM disorders and cause-specific mortality in adulthood. Therefore, these variables were included as covariates. As a measure of socioeconomy the father's and mother's education were graded in seven levels. Age was also adjusted for in all models.

For a sub-cohort of men who enlisted during 1969–1970 (n=49 571), data on smoking was recorded. The conscripts completed a questionnaire regarding numbers of cigarettes smoking per day, alcohol and drug habits [72].

Outcome assessments during the follow-up period

The outcome variable cause of death was specified as causes of death classified according to ICD as shown in Table 4.

Statistical methods Study II

To assess the influence of NPM disorders at conscription on cause-specific mortality, Cox proportional hazards models were used. Subjects were followed until time of: 1) death, 2) emigration or 3) end of follow-up.

Population-attributable risk (PAR), the association of a specific risk factor with a specific outcome as a proportion of all risk factors for that outcome, was calculated by the method of Natarajan et al using the HRs from the Cox proportional hazard regression models [73].

Table 3. *Diagnostic categories, frequencies and ICD-codes for NPM disorders, Study II.*

Diagnostic category	ICD-8	ICD-9	ICD-10
No Non-psychotic mental disorders (NPM) (n= 1 710 101)			
Non-psychotic mental disorders (NPM) (n = 74 525)			
Depressive and neurotic/adjustment disorders (n=57 708; 2940/54 975)	296.0, 296.2, 298.0, 300.4/300.0-3, 300.5-9, 305, 307	298.0, 300.4, 311/300.0-3, 3005-9, 306, 308-9	F32-34, F38-39/F40-48
Personality disorders (n=10 567)	301	301	F60-69
Alcohol-related/other substance use disorders (n= 8644; 3394/5691)	291, 303/294.3, 304	291, 303, 305.0/292, 304, 305.1-8	F10/F11-19

Table 4. *ICD-codes and frequencies for cause-specific mortality, Study II.*

Causes of death (n=54 918)	**ICD 8**	**ICD 9**	**ICD 10**
ALL NATURAL CAUSES (n=30 959)	000-795	001-797	A00-R99
Infectious diseases (n=673)	000-136	001-139	A00-B99
Neoplasms (n=11 076)	140 –239	140 –239	C00–D48
Diseases of the circulatory system (n=9336)	390–458	390–458	I00 –I99
Diseases of the respiratory system (n=1075)	460-519	460-519	J00-J99
Diseases of the digestive system (n=2132)	520-577	520-577	K00-K93
Unspecified natural causes (n=6667)	240-389, 459, 578-797	240-389, 459, 578-797	E00-H99, L00-R99

3.2 METHODS - STUDY PROTOCOL RCT

Between May 2017 until May 2021 we performed a parallel RCT called PHYSBI –Physical Fitness and Brain, an exercise interventional study of the importance of cardiovascular fitness on symptoms of anxiety and cognitive ability in patients with anxiety disorders. The patients were recruited within primary care in Region Västra Götaland and Region Halland. The study included three assessment points (baseline, post-intervention and one-year follow-up). The study was registered as a clinical trial in August 2017, see https://clinicaltrials.gov/ct2/show/NCT03247270.

Participants aged 18 – 65 with symptoms of anxiety were randomly assigned to an exercise program with two different exercise intensity or a control group. Assessments were performed at Askim (Sisjöns) Primary health care center in Gothenburg. Interventions were conducted at Primary Care Rehab (Närhälsan Primary Care, Gothenburg, Sweden) and at a fitness center ("Friskis and Svettis") in Gothenburg.

A GP or psychologist recruited individuals presenting with symptoms of anxiety. These individuals were informed both verbally and in writing, and those who accepted participation signed a written informed consent. At baseline assessment, before decision of inclusion, the study physician evaluated information about physical comorbidities and the study psychiatrist diagnosed the various anxiety disorders and mental comorbidities using the Mini International Neuropsychiatric Interview (M.I.N.I; Swedish version 6 and 7.0.0) a structured diagnostic interview with high reliability and validity [74].

3.2.1 STUDY DESIGN STUDY PROTOCOL

Participants and inclusion/exclusion

Patients diagnosed with anxiety disorders, including panic disorder (F41.0), generalized anxiety (F41.1), mixed anxiety- and depression conditions (F41.2 and F41.3), as well as anxiety UNS (F41.9) were included in the study. To preserve statistical power for the analyses, patients with above mentioned anxiety disorders were grouped together and denounced as patients with anxiety disorders.

Patients with physical difficulties in performing a physical exercise program, pathological electrocardiogram (ECG), previous psychiatric illnesses, ongoing abuse, ongoing burn-out syndrome, as well as patients who are using beta blockers were excluded from participation. Pregnant women were also excluded. Another exclusion criterion was high suicide risk. Individuals with serious neurodevelopmental or psychotic disorders were excluded (milder cases were included) as assessed by the study GP or psychiatrist according to MINI at baseline. Baseline physical activity level exceeding one exercise occasion per week and ongoing psychotherapy were exclusion criterions. The rationale for this was that psychotherapy was viewed as a regular treatment and also an engagement in terms of time and energy which could impact on adherence to the intervention. However, ongoing treatment with psychoactive medication was not an exclusion criterion.

Intervention

Recruited patients were randomized into three groups:

1) A 12-week exercise program with low-intensity fitness training three times per week for one hour. Intensity corresponded to 1.5 – 2.9 metabolic equivalents (METs) / Borg rated perceived exertion (RPE) 10-14 / 40-59% of maximal heart rate.

2) A 12-week exercise program with moderate to high-intensity fitness training three times per week for one hour. Intensity corresponded to 3.0-8.9 METs / Borg RPE 12-17 / 60-94% of maximal heart rate.

3) Control group with a single physiotherapy session and general advice according to national recommendations about physical activity. Participants in the control group received a training card for three months after study completion.

The study physiotherapists personally designed the exercise program in the gym and had one-to-one sessions with each participant on two occasions. Participants in the intervention groups exercised separately in group-sessions

with the physiotherapist according to a pre-determined program. Both intervention groups contained cardiorespiratory and resistance training.

The exercise program was designed as a circuit training with 12 stations. It also included 10 min of warm-up and 5–10 min of cool down and stretching exercises. Cardiorespiratory exercises included step-ups, step on step board, jump rope, step touches side-to-side and burpees. Resistance training exercises included squats, push-ups, abdominal plank position, row exercises, hip lifts and crunches.

A pulse-watch and rating of the Borg RPE scale were used to monitor level of exertion and to ensure appropriate exercise intensity. If patients were unable to participate at a group session, pre-determined replacement exercises were performed on their own.

Assessments

Participants were assessed at baseline, post-intervention and at one-year follow-up by the study physician, psychiatrist and psychologist. The assessments included mental health variables such as psychiatric diagnoses at baseline and severity of perceived symptoms of anxiety and depression using the established self-assessment scale Beck Anxiety Inventory (BAI) [29] and the Montgomery Åsberg Depression Scale (MADRS-S) [75]. For BAI, both reliability [30] and validity [31] are reported to be high. Furthermore, BAI mainly evaluates somatic symptoms for example tremor, experience of palpitations in heart, dizziness and was developed to be relatively free from depressive content. It is organized in 21 items, each rated as follows: symptom not present (0 p), slight (1 p), moderate (2p) and severe (3p). Total ratings were trichotomized (nothing, minimal/mild (score 0–15), moderate (score 16–25) or severe (score 26–63).

MADRS-S scores were categorized as no/minimal depression (score 0–12), mild (score 13–19) or moderate (score 20–34). We also analysed MADRS-S item 2 as it provides a rating of anxiety (inner tension). Psychoactive prescription drugs, including antidepressants, with dosage and duration were reported by the patient at each assessment point. Physical health variables such as blood pressure, height and weight including body mass index (BMI) using weight in kilograms (kg) divided by the square of the height [76] in meters (m) were collected for each patient at each assessment point. The same was the case for alcohol use, rated with the Alcohol Use Disorders Identification Test (AUDIT) [77]. Every patient self-reported marital status, educational level, years with anxiety symptoms, dietary habits, smoking, comorbidities, use of other prescribed drugs and physical activity in a questionnaire designed by our research team. Experienced health and perceived quality of life were measured using the EuroQol-5 Dimension Questionnaire (EQ-5D), a standardized

question and scale measurement covering five dimensions: anxiety/depression, usual activities, mobility, self-care and pain/discomfort [76].

We used The Wechsler Adult Intelligence Scale, 4th edition (WAIS-IV) to measure cognitive functions and intelligence. This test battery is stratified to match a Scandinavian population based on sex, age, ethnicity, education and geographic region and standardized against a normative sample of individuals between ages 16 to 90 years. The tests includes scaled scores from 1 to 20 with a normed mean of 10 and standard deviation (SD) of 3 [78]. In the current study the digit span, block design and matrix reasoning tests were used. Full WAIS-IV assessment was not possible to execute due to the long completion time.

To measure EF, working memory, attention and mental manipulation as encoding and auditory processing, we used the digit span test. The digit span forward subtest primarily measures short-term memory and attention [79]) and the digit span backward subtest measures WM. The digit span sequencing subtest captures functions such as cognitive flexibility [78].

To measure visual-spatial perception and nonverbal problem-solving skills we used the block design test. Participants had to replicate red and white pattern designs using three-dimensional coloured blocks. Although also capturing dimensions of EF such as problem-solving and reasoning [80-82], the block design test is mainly used as a measure of fluid intelligence [79].

In the matrix reasoning test individuals had to solve a problem presented in a visual format and recognize forms and patterns in designs [78]. This test includes visuospatial ability, perceptual reasoning and non-verbal problem-solving and is often used as a measure of fluid intelligence. As for the block design test, the matrix reasoning test also involves problem-solving and reasoning.

Further measurements of cognitive function included The Delis-Kaplan Executive Function System (D-KEFS). D-KEFS is a standardized, non-verbal psychomotor test battery measuring EF in patients between ages 8 to 89 years [83]. The D-KEFS normative sample included over 1700 children, adolescents and adults, and was based on demographic characteristics (including gender, age and socioeconomic factors) of the U.S. population [83, 84]. We used the subtest design fluency, which simulates the cognitive ability required in everyday life to render responses, while maintaining focus on a demanded goal, and assesses processes such as creativity, inhibition of responses and cognitive flexibility [84]. It consists of three stipulations, performed with paper and pen and where participants are instructed to bind together dots and make as many new shapes as possible during one minute.

In addition to the requirement for cognitive flexibility in doing these tests the participants also need to use working memory and scanning skills to remember

hitherto drawn shapes and inhibit the instinctive need to repeat shapes and use creativity to find previously unknown solutions to the task.

The total number of correct patterns and number of total patterns within the one-minute time limit were registered for each stipulation and raw scores from each subtest were changed to age-adjusted scaled scores ranging from 1 to 19 with mean 10 and SD 3.

For measuring EF both in clinical and research settings D-KEFS test battery has showed good reliability and validity [84]. All cognitive tests were applied by a licensed psychologist. All participants performed the WAIS-IV tests before the D-KEFS test.

Physical fitness test

Åstrand's submaximal ergometer test was used to measure cardiovascular fitness and maximal oxygen uptake capacity (VO_2max) [85]. Physiotherapists at Primary Care Rehab in Gothenburg, who also were responsible for the training sessions, performed the testings. The ergometer was calibrated for each patient and heart rate was adjusted for age and sex. Predicted $V0_2max$ was calculated according to the nomogram described by Åstrand and Rhyming [85]. A previously used test of maximum number of one-leg rises from sitting on a chair (45 cm high) during 1 min was used to measure muscle strength [86] The patient was told to keep the arms crossed and to hold the other leg extended without touching the floor, and to perform the test at a constant speed.

Adverse events

Exercise participation requiring medical intervention care were reported on two occasions during the intervention:

1) one participant in the moderate to high-intensity exercise group evolved symptoms of exhaustion disorder

2) one patient incurred a spinal disc herniation at L5-S1 when lifting a bench just after a training session.

After the first occasion a baseline screening with a self-assessed questionnaire for exhaustion disorder [87] was added in the autumn of 2019. The second event was not regarded preventable and resulted in no change of the study design.

3.3 METHODS (STUDY IV AND V)

Studies IV and V were based on the RCT PHYSBI, an interventional study. For detailed study design see Study protocol.

3.3.1 STUDY DESIGN STUDY IV

In Study IV, a cross-sectional study, we included 189 Swedish patients from primary care, aged 18–65 years (69 % women) with anxiety disorders diagnosed with PD, GAD and/or anxiety NOS according to M.I.N.I. The patients were included and deriving from the interventional study PHYSBI during 2017 - 2019. Inclusion and exclusion criteria followed the PHYSBI Study Protocol. The aim was to evaluate cross-sectional associations between cognitive function, with focus on executive function, and severity of anxiety. Anxiety severity was assessed using BAI, dichotomized as minimal/mild (BAI 0–16) and medium/severe anxiety (BAI 17–63). Cognitive function was measured using the WAIS IV tests and the D-KEFS design fluency test, employed by a licensed psychologist according to Study Protocol for PHYSBI.

Statistical method Study IV

For this study we used a multivariable linear regression model to investigate the relationship of anxiety severity and cognitive functioning using self-reported BAI scores and performance scores in the cognitive test battery described in Study Protocol. The current study design did not involve a group of persons without anxiety disorders for comparison. Therefore, also analyses for comparing cognitive functions in individuals with anxiety disorders to an age-adjusted normed population were performed, using the Wilcoxon signed rank test, with standard algorithms (with a normed mean of 10, and an SD of 3 for all tests) [78, 84]. This method has been used before for measuring cognitive function in young men [88]. In multivariable models we analysed covariates including age, gender [89], smoking [90-92], educational level and comorbid major depression (assessed through M.I.N.I.). Additional regression analyses were performed comparing patients with minimal/mild (BAI 0-16) and medium/severe (BAI 17-63) anxiety [93]. This method has been used previously for measuring cognitive function in young men [88].

3.3.2 STUDY DESIGN STUDY V

Study V is a randomized controlled trial, where we investigated, according to previously described Study Protocol, if a group exercise program, with different intensities, could reduce symptoms of anxiety in patients with anxiety disorders. 286 participants were recruited during 2017 to 2021. Severity of symptoms was self-assessed using BAI, MADRS-S and MADRS-S question 2. Participants were randomly assigned to one of two group exercise programs and one control non-exercise group, with 1:1:1 allocation.

Assessments were collected at baseline and at 12-week (post intervention). The outcome was improvement in anxiety measured with BAI and MADRS-S question 2. Cardiorespiratory fitness and muscle strength were measured using standardized tests according to the Study Protocol. For half of the included patients, intervention group was double-blinded to both researchers and patients. For the other half, intervention group was only blinded to the researchers, while patients were aware of the exercise intensity group.

Statistical methods Study V

A statistician performed a power analysis before study initiation, see Study Protocol. To allow for expected drop-outs and achieve an adequate number of study participants we recruited 25% more participants than required.

Changes between baseline and post-treatment were presented as means with corresponding CIs. Our main outcome variables were changes in BAI, MADRS-S and MADRS-S question 2 between baseline and postintervention at 12 weeks. In order to measure the overall treatment effect i.e. effect size of the two intervention groups vs. the control group, we used analysis of covariance (ANCOVA) in a general linear model, calculating an unstandardized mean difference. In order to also measure the standardized effect sizes we used the Cohen's d to compare mean differences.

In this study, BAI and MADRS-S scores were dichotomized with the mean change in the control group as reference. We defined improvement in anxiety symptoms as a between-group difference (improvement) of 5 points on the BAI scale, based on the mean difference in BAI scores between baseline and post intervention for the control group. For depression symptoms, measured with MADRS-S, we used a difference (improvement) of 3 points, which corresponds to the mean improvement of the control group.

To study a clinically relevant improvement these dichotomies were then used for binary logistic regression with multivariable adjustments and expressed as odds ratios (OR).

In a corrigendum we also report effect sizes in standardized Cohen´s d (see figure 7).

3.4 STATISTICAL ANALYSES

Table 5 shows an overview of the statistical methods used in this thesis. No statistical analysis were used in Study protocol (Study III).

Table 5. *Statistical methods*

	Study I – prospective cohort	**Study II – prospective cohort**	**Study IV – cross sectional**	**Study V – RCT**
Statistical model	Cox proportional hazards models	Cox proportional hazards models, Poisson regression (for incidence rates and confidence interval)	Multiple linear regression analyses	Power analysis. For effect size ANCOVA in a GLM, generating an unstandardized mean difference. ORs from binary logistic regression with multivariable adjustments in various models. Effect sizes in standardized Cohen´s d
Analysis time scale	Time in study (3- 42 years) 1971-2010	Time in study, (3-42 years) 1968-2014	At five different time points, 2017-2019)	Time in study, 2017-2021
Covariate adjustment	Conscription calendar year and region, BMI, parental education, IQ	Age, conscription decade, test center, parental education, systolic/ diastolic BP, cardiovascular fitness, BMI, IQ	Education, smoking, age, gender and comorbid major depression	Sex, age, baseline psychoactive medication, major depression, BAI-score, cardiovascular and respiratory disorders, smoking and physical exercise
Handling of missing data	Exclusion	Exclusion	No missing	No missing
Other statistical methods		Population-attributable risk (PAR)	Different multivariable models	Correlation matrices and multivariable binary regression analyses for mediator analysis

3.4.1 COX PROPORTIONAL HAZARD MODELS

A statistical method in survival analysis is the Cox proportional hazards regression analysis [94], which can be used for both quantitative (continuous) predictor variables and for categorical variables (binary, nominal or ordinal). Furthermore, the Cox regression models can assess the effect of several risk factors on survival time.

The probability used to describe survival data in the Cox model is the hazard ratio. It allows us to explore how specified factors influence the rate of a special event happening (for example a mental disorder or death) at a particular point in time for an individual who has survived or survived without experiencing failure.

The Cox model assumes proportional hazards (PH) meaning that the hazards can vary over time but when comparing groups, the HR in one group remains proportional to the hazard in the other group over the follow-up time, or equivalently that the relative hazard remains constant over time. The PH assumption can be validated in different ways. One easy way is to check for the occurrence of crossing Kaplan-Meier curves; another is to use a graphical method and plot log-log survival curves. Two other options are to stratify for different covariates of interest, as a way to control for potential confounding or to use another model for survival analysis, for example a Poisson regression.

Confounding

In epidemiological studies you often have to take additional factors into account and not only one factor or exposure. To evaluate the effect of the exposure of interest, other factors associated with both the exposure (as age and gender for example) and the outcome (for example death or psychiatric illness) also needs to be considered. We call these factors confounders [95] and they are characterized by:

- Ought to be related with the outcome as a risk factor/as a cause, but not as an effect of the outcome
- Ought to be related with the exposure
- Can´t be a part of a causal pathway

Furthermore, in clinical trials there are many different ways that relationships between variables we are interested in can be expressed. In our intervention and statistical calculation there is an independent variable or predictor and an outcome as a dependent variable. These can be influenced by a third variable, that we have considered, or not have considered, such as a confounders or covariates.

When searching for the etiological importance of variables or causal relationship, confounding can obscure the real effect of an exposure. There is a risk for both over – and under-estimating the true effect. Confounding can be

prevented by use of randomization (individuals are chosen by chance in two or more groups), restriction or matching (individuals with same characteristics for example gender are selected one to one into groups). Using stratification or multivariate analysis after completion of a study is another way to control for confounding. The criteria for a possible confounder are important to consider before adjusting for confounding to prevent the introduction of possible new bias through overadjustment.

However, a major limitation of observational cohort studies is the lack of causal inference i.e. that the association detected between an exposure and an outcome may not imply a causal relationship.

3.4.2 ANCOVA AND BINARY LOGISTIC REGRESSION

Logistic regression is utilized when the outcome variable is binary, but he input variables can be either binary or continuous. Linear regression is used to describe the relationship between two variables where one variable (the dependent variable) is expected to change as the other one (independent, explanatory or predictor variable) changes. Multiple regression allows many variables to be explored at the same time, with one outcome variable.

A general linear model which uses ANOVA (analysis of variance) and regression models are analysis of covariance (ANCOVA). ANCOVA estimates whether the means of a dependent variable are equal across levels of a categorical independent variable, often a treatment, while controlling for the effects of other variables that are not of primary interest.

Effect sizes are defined as a numerical quantification of the strength or effect of a predictor on an outcome variable [96]. Literature on how to scientifically reported effect sizes promote different and sometimes conflicting perspectives based on the scale or metric of the effect size, as unstandardized or standardized values. It has been proposed that reporting the better understood and less controversial unstandardized effect sizes is more suitable for primary research, which is consistent with the recommendations of the APA Task Force on Statistical Inference [96]. However, the extent or impact of an effect should be evaluated by its practical significance. Sometimes it is more meaningful to use the simple mean differences.

3.5 ETHICAL CONSIDERATIONS

The epidemiological Studies I and II were approved by the Ethics Committee of the University of Gothenburg (Table 6) and the Confidentiality Clearance at Statistics Sweden. Since these studies were register-based and resulted in completely decoded data for over a million individuals, our consideration was that no intrusion into privacy should occur.

Table 6. *Ethical approvals.*

	Ethical Review Board (EPN)	Diary number (DNR)	Added
Study I	Gothenburg	462-14	T653-17
Study II	Gothenburg	462-14	T653-17
Study III	Gothenburg	300-16	T241-17, T1008-18
Study IV	Gothenburg	300-16	T241-17, T1008-18
Study V	Gothenburg	300-16	T241-17, T1008-18

For Studies III-V we had ethical (Table 6) and biobank (No 946) approval to carry out the RCT. Recruited patients were informed both verbally and in writing about the purpose and the study design including randomization, the importance of active participation for reliable data and the possibility of ending their participation at any time. Each participant had to sign a statement of informed consent before study inclusion. Coding and anonymization of data occurred after data collection was completed. All data analyses were performed on coded data presented on group levels. The database is stored in a locked archive at Gothenburg University.

A minor risk for injury while exercising existed, such as a sprained muscle. To minimize the risk for this, competent primary care physiotherapists designed and modified the exercise program according to the ability of each participant. To minimize the risk for worsening mental health during the intervention, the following precautions were made:

1. A GP assessed suitability for study participation
2. Patients with high suicide risk were excluded
3. All intervention staff were trained in the recognition of symptoms of anxiety and depression
4. Mental health was continuously monitored by the study physician and adverse events were recorded and evaluated

All studies in this thesis conformed to the principles outlined in the Declaration of Helsinki.

4 RESULTS

4.1 ASSOCIATION BETWEEN CARDIOVASCULAR FITNESS AND RISK OF NON-AFFECTIVE DISORDER (STUDY I)

In this study (for design see Table 1) the mean follow-up time was 25 years. During the follow-up period, in total 27 528 903 person years, 17 262 men were diagnosed with neurotic, stress-related and somatoform disorders and 10 205 men were diagnosed psychotic disorders.

During follow-up, 55 697 individuals died or emigrated. In individuals diagnosed with schizophrenia, other comorbid psychotic disorders were found in almost 50 %, and almost 20 % had comorbid neurotic, stress-related, and somatoform disorders.

The analysis showed a higher risk for individuals with low cardiovascular fitness compared to high regarding schizophrenia. Low cardiovascular fitness showed a HR of 1.44 (95% CI 1.29–1.61) compared to high fitness in fully adjusted models at age 18. Corresponding HR for neurotic or stress-related and somatoform disorders was HR 1.45 (95% CI 1.37–1.54).

In total 492 070 individuals in the study were identified with one or more full brothers in the cohort. Approximately 5000 of those individuals developed psychotic disorders: and 7848 developed neurotic, stress-related, and somatoform disorders during the observation period. Sub-analyses of this group with one or more brothers affected with outcome diagnosis, showed that all relationships persisted in models also adjusting for familial factors.

4.2 ASSOCIATION BETWEEN NPM AND MORTALITY (STUDY II)

In this study we followed 74 525 men diagnosed with NPM disorders prior or at enlistment. During follow-up the study encompassed 45 872 922 person-years. Baseline characteristics showed that those with NPM disorders had lower level of parental education, slightly lower weight, lower IQ scores and poorer cardiovascular fitness compared to men without NPM disorder. Median follow-up time for the whole cohort was 26 years. During the follow-up, approximately 55 000 men died and 110 000 emigrated. Among those men with NPM disorders at conscription, 77% had a depressive and neurotic/ adjustment mental disorder where neurotic/adjustment disorders were the most frequent. Furthermore, alcohol use disorders were less frequent than other substance use disorders. A Venn diagram visualizing diagnostic overlap is shown in figure 6.

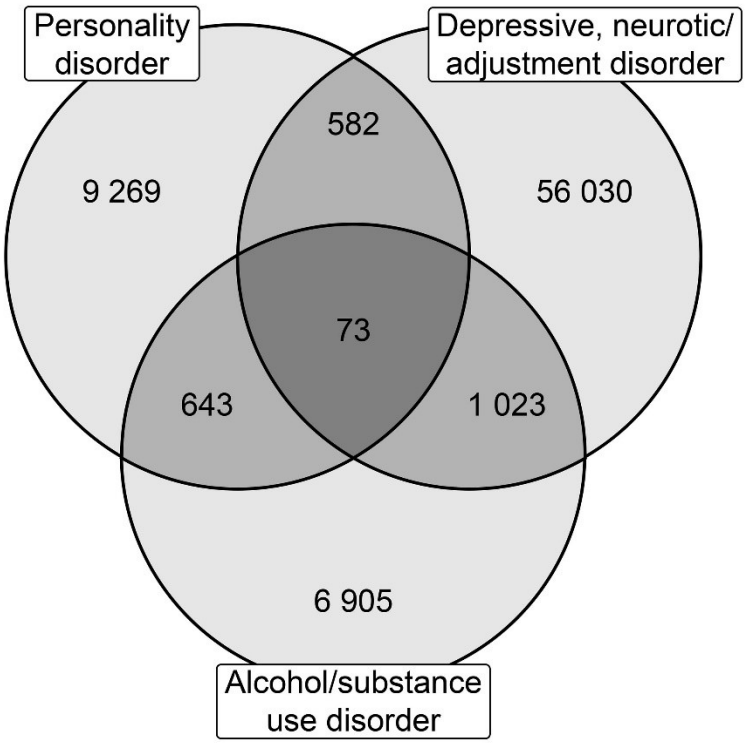

Figure 6. Venn diagram showing the diagnostic overlap of the three categories of baseline non-psychotic mental (NPM) disorders. Printed with permission of the author.

All-cause mortality

Of those with NPM disorders, 10% (n=7390) died during follow-up compared to approximately 3% of those without NPM disorders. NPM disorders at baseline, in age-adjusted models, were associated with more than a twofold increase in all-cause mortality risk. Subgroup analysis by diagnostic subgroup revealed the highest risk for alcohol/substance use disorders. Mortality risk associated with depressive/neurotic disorders were lower compared to those with personality disorders.

Cause-specific mortality

There was no difference between men with and without NPM regarding death of natural causes during follow-up. However, deaths by infectious diseases and diseases of the digestive system were twice as common in men with NPM disorders. Examining depressive, neurotic/adjustment, alcohol/substance use and personality disorder separately showed similar trends in proportions of deaths by natural causes.

When analysing specific mortality causes separately, for all NPM disorders combined, the strongest association was observed for death due to infectious diseases with over a three-fold increased risk in the fully adjusted model.

When analysing the three diagnostic NPM disorder subgroups separately, risks in fully adjusted models were elevated for death by infectious diseases with HRs ranging from 2.07 to 2.90 for depressive/neurotic/adjustment disorders and personality disorders, respectively. Alcohol-related and other substance use disorders were associated with the highest risk, HR 9.02 (95% CI 6.63 to 12.27). HRs for death by gastrointestinal causes was also high in all three diagnostic subgroups ranging from 1.64 to 4.41.

Population attributable risk (PAR)

NPM disorders at conscription and mortality due to infectious diseases had the highest PAR (15.5%) when analysing the different causes of death separately.

4.3 COGNITION (STUDY IV)

In this cross-sectional study we included 189 patients after baseline assessments for PHYSBI. See Paper 4 for baseline characteristics of the sample of patients with anxiety disorder. Mean BAI score was 25 (SD 13), which correlates with moderate/severe anxiety. 53% of the participants reported an onset of anxiety more than 10 years ago.

When analysing the associations of anxiety severity and cognitive performance significant associations were found for several subtests, see Table 7. However, in analyses with further adjustment for comorbid major depression, anxiety scores only associated with scores for the digit span total subtest. Additional statistical analyses comparing cognitive function of individuals with moderate/severe anxiety (n=128) to individuals with minimal/mild anxiety (n=61) revealed that those with moderate/severe anxiety scored lower on the digit span total subtest (Table 7).

When comparing to a normed non-clinical population in cognitive function individuals with anxiety disorder performed significantly worse than a normed population on the block design, digit span forward and sequencing, and matrix reasoning tests. However, individuals with anxiety disorder performed better on all the design fluency tests.

Table 7. *Association of anxiety severity (BAI score) and cognitive function test scores, also adjusting for depression.*

Cognitive function test scores	B	r	Equation	R^2	P value
WAIS-IV tests					
Block design	-0.036	0.467	F(3,168)=7.761	0.190	0.050
Digit span total	-0.040	0.331	F(6,177)=3.623	0.109	**0.018**
Digit span forward	-0.038	0.277	F(6,167)=2.316	0.077	0.076
Digit span backward	-0.045	0.299	F(6,167)=2.736	0.089	**0.008**
Digit span sequencing	-0.030	0.280	F(6,167)=2.363	0.078	0.091
Matrix reasoning	-0.032	0.373	F(6,164)=4.426	0.139	0.063
D-KEFS design fluency					
Total correct designs	-0.019	0.322	F(6,175)=3.367	0.103	0.261
Correct designs condition 1	-0.014	0.330	F(6,175)=3.555	0.109	0.413
Correct designs condition 2	-0.028	0.305	F(6,175)=2.988	0.093	0.090
Correct designs condition 3	-0.011	0.258	F(6,175)=2.076	0.066	0.499
Total attempted designs	-0.020	0.334	F(6,175)=3.653	0.111	0.337

Comorbid major depression, education, smoking, age and gender as covariates.
Statistically significant results (p>0.05) indicated in bold.

4.4 12-WEEK OUTCOME ANXIETY (STUDY V)

This study included 153 individuals with anxiety disorder, who were followed until 12-weeks post-intervention assessments in PHYSBI. Among these individuals cardiovascular fitness was markedly lower compared to the Swedish population and 15% reported daily tobacco use [97]. Participants had a high proportion of hazardous alcohol use according to AUDIT and BMI indicated overweight [98]. At baseline, approximately one quarter were on sick leave and almost two thirds were on psychoactive medication. Adherence rate in both exercise groups were 70%. The response rate at post-intervention was 69% (including controls). The drop-out frequency was similar in all three groups.

Compared to the control group, a significant reduction in our primary outcome, anxiety symptoms from baseline to post-treatment, was observed in both intervention groups. While anxiety levels at baseline in most patients correlated with moderate to severe anxiety, anxiety levels at follow-up correlated with mild anxiety in both treatment groups, see figure 7. The effect sizes are expressed as an unstandardized mean difference and for comparison as standardized effect sizes, expressed by Cohen's d, presented in a published Corrigendum.

Descriptive frequencies for the dichotomized BAI variable (improvement/no improvement) showed that approximately 65 % of the patients improved their symptoms of anxiety in both intervention groups. For low-intensity exercise the OR for ameliorated symptoms of anxiety was 3.62 (CI 1.34–9.76) and for moderate/high intensity 4.88 (CI 1.66–14.39) with a significant intensity trend (p=0.003), all in fully adjusted models.

Level of inner tension (MADRS-S item 2) was lower post-intervention in the moderate/high intensity exercise group compared to the control group. Comparing low intensity exercise with the control group for improved inner tension showed OR 2.21 (CI 0.92–5.3) in fully adjusted model, and after moderate/high intensity exercise 4.21 (CI 1.61–11.02).

On symptoms of depression, our secondary outcome, individuals in both exercise intervention groups also improved, see figure 7. Descriptive frequencies for the dichotomized MADRS-S variable (improvement/no improvement) showed improvements in depression symptoms (MADRS-S) for 77% of the participants in low intensity group and for 70% in the high intensity group. In the final adjusted model, the low intensity group was associated with a more than five-fold increase in the odds ratio of symptom improvement compared to the control group. A four-fold increase in odds ratio was observed for the moderate/high intensity group compared to the control group.

Compared to control group, mean muscle strength increased significantly in both intervention groups. Cardiorespiratory fitness level also showed improvements post intervention in both intervention groups, but these were all non-significant.

Sensitivity analyses for all outcomes described above in which participants who had initiated a pharmacotherapy during the intervention period were excluded did not attenuate the results.

Stratification for the two blinding procedures revealed no indication of bias. Alterations in cardiorespiratory fitness (VO_2max) or muscle strength did not correlate with alterations in anxiety or depressive symptoms.

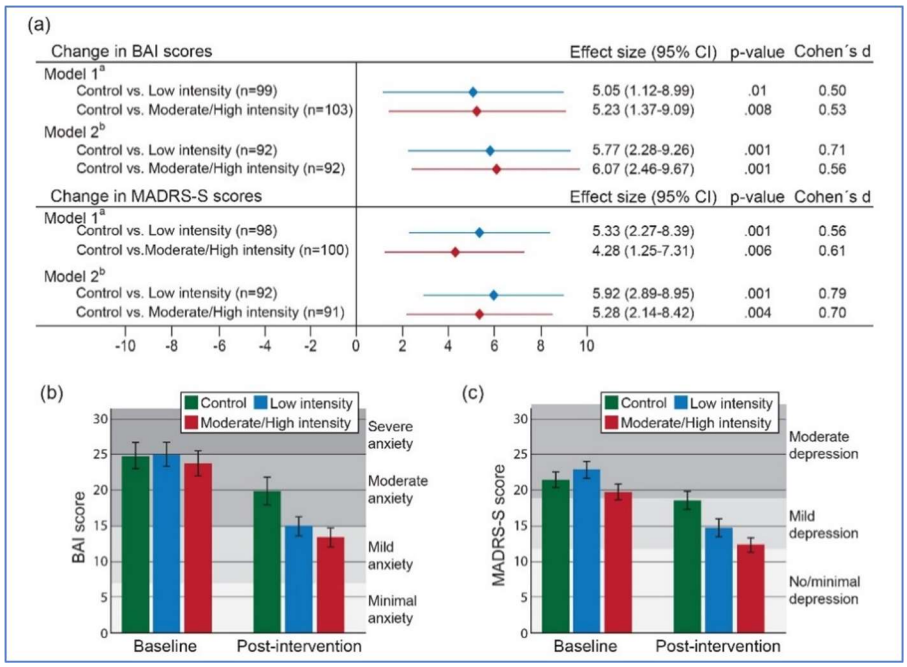

Figure 7. Between-group treatment effects on self-rated anxiety symptoms (BAI scores) and depression symptoms (MADRS-S scores) Effect sizes are shown as both unstandardized and for comparison the standardized mean differences, expressed by Cohen's d. Mean BAI (b) and MADRS-S (c) scores at baseline and at post-intervention by exercise intervention group. Severity levels for anxiety (b) and for depression (c) are indicated in shades of gray. Model a) Adjusted for sex and age; b) Adjusted for sex, age and baseline psychoactive medication, major depression, BAI-score, cardiovascular and respiratory disorders, smoking and physical exercise at baseline. Adjusted and printed with permission of the author.

5 DISCUSSION

The aim of this thesis was to study mental disorders and the association with cause-specific mortality and the importance of cardiovascular fitness both regarding prevention and intervention. The main findings are that lower cardiovascular fitness in 18-year-old men is associated with increased risk of serious non-affective mental disorders in adulthood and that young men diagnosed with NPM disorders have a long-term increased mortality risk. Furthermore, we found that physical exercise represents an effective treatment for persons with anxiety disorders within primary care.

5.1 Findings and implications

Low cardiovascular fitness and risk for non-affective mental disorders

In our studies we found that low premorbid cardiovascular fitness in late adolescent males were prospectively associated with an increased risk of schizophrenia as well as with anxiety and stress related disorders, also after adjusting for confounders including familial factors. Low and medium (compared to high) cardiovascular fitness increases the risk for future schizophrenia and schizophrenia-like disorders as well as for other psychotic disorders with similar HRs for these categories, indicating a high degree of diagnostic overlap.

Defining cardiovascular fitness is important as it´s not equivalent to physical activity and is considered to be a potential modifiable target for prevention. It is defined as “the overall capacity of the cardiovascular and respiratory systems and the ability to carry out prolonged vigorous exercise” [99]. On the other hand physical activity is defined as “any bodily movement produced by skeletal muscles that result in energy expenditure” [100].

A meta-analysis has demonstrated that individuals with schizophrenia has a severely reduced cardiorespiratory fitness compared to age- and sex-matched controls [101]. Moreover, a relation between reduced cardiovascular fitness and stages of illness in psychotic disorders has been reported [102] also compared to healthy controls. A meta-analysis of clinical RCT´s supports evidence for a positive effect of physical activity in reducing symptoms of schizophrenia as well as improved aerobic capacity and quality of life among individuals with schizophrenia [103]. Another meta-analysis provides evidence that exercise can improve overall cognitive abilities such as attention, working memory and social functioning among individuals with schizophrenia, especially from interventions using exercise of higher intensity [104]. Cardiovascular fitness during puberty might affect the risk of schizophrenia through different mechanisms in the brain. Imaging studies of the brain have shown that patients with schizophrenia have a smaller volume

of amygdala-hippocampal complex and prefrontal cortex [105], smaller thalamus and greater ventricular volumes compared to healthy controls. There is a possibility that prodromal symptoms of psychotic disorder decrease the level of physical activity for these individuals since poor motor function is an early sign of schizophrenia [106] and can partly explain a lower cardiovascular fitness. Furthermore, young individuals diagnosed later in life with schizophrenia are shown to be less physically active in the stage before diagnosed, compared with healthy controls [107]. Moreover, we could not adjust for the degree of social functioning which might be compromised in young people who later develop schizophrenia. This is a drawback since social functioning may affect participation in physical activities and thereby cardiovascular fitness at conscription.

We also reported a relationship between low cardiovascular fitness and increased risk for future neurotic or stress-related disorders. A recently published population-based (n=400,000) study found that having a physically active lifestyle as a skier, was associated with 60% lower risk of developing anxiety disorders, compared to matched, non-skier, healthy controls [108]. This study followed almost 400,000 individuals up to 21 years and also included women, in contrast to our studies. Furthermore, our study shows similarities to a previous, both cross-sectional and prospective population-based study, demonstrating shorter term (4 year) risk of developing anxiety disorders, including post-traumatic stress disorders, in persons with self-reported low physical activity [109]. Our findings parallel those of a meta-analysis that showed a prospective association between physical activity and anxiety disorders [110]. In our study we could not find any association, in fully adjusted models, between low cardiovascular fitness and risk for somatoform and dissociative disorders indicating that confounders might influence those associations.

We also found that familial factors, such as having a brother diagnosed with the specific disorder, had a large effects on risks for developing future schizophrenia and schizophrenia-like disorders, other psychotic disorders neurotic and stress-related and somatoform disorders. However, the risks for these mental disorders associated with having a lower cardiovascular fitness still remained significant in analyses taking familial factors into account.

Our study demonstrates significant associations between low cardiovascular fitness in young age and later risk of non-affective mental disorders. These results highlight the importance of early preventive strategies in increasing cardiovascular fitness in adolescence and reducing the risk for later non-affective mental disorder.

NPM-disorders and cause-specific mortality risk

We found that men with NPM disorders in late adolescence had a long-term increased mortality risk, especially due to gastrointestinal and infectious diseases. Previous longitudinal studies are lacking for comparison. Possible explanations behind the increased mortality for natural causes in men diagnosed with NPM disorders include physical inactivity, heavy alcohol use, smoking, unhealthy diet, and inadequate treatment for physical conditions [111-113]. Adjusting for IQ, smoking and cardiovascular fitness at conscription only slightly attenuated the strength of the associations. These results are in line with a previous study analysing NPM disorders and all-cause mortality in a prospective cohort study, which indicated that higher IQ may act as a possible resilience factor against future mortality [6].

The relationships of alcohol and substance use with mortality due to infectious diseases are well known [111, 114] but less is reported regarding anxiety, depression and personality disorders. Our results that early onset of those disorders increase the risk of death by infectious diseases expands on previous studies employing both short follow-up time, both sexes and mixed age populations [111, 115-117]. On the other hand, self-reported chronic anxiousness (subclinical anxiety) in German adults did not predict all-cause mortality in a recent population-based observational study with over 11 000 participants [118]. In our study, only 1/7 of the deaths by infectious diseases were related to HIV and was therefore underpowered to investigate the previously reported strong association between HIV and anxiety and depression [116].

HRs reported in our study are higher than those earlier reported for death by infectious disease. This may be due the fact that infection mortality decrease with increasing age [119] and our study population is relatively young.

When analysing the different causes of death separately, mortality due to infectious diseases in NPM disorders at conscription had the highest PAR (15.5%). The second highest PAR estimates were observed for mortality due to diseases of the digestive system. The use of PARs can indicate the magnitude of a risk factor. As we cannot make conclusions about causality, PAR is a way of calculating the proportion of the incidence of a disease, in the population (exposed and non-exposed) that is due to exposure, in this case NPM-disorder [120].

Our results indicate that young men with NPM disorders are vulnerable, pointing out the importance of including this age group as a public health priority to prevent premature death.

RCT Study Protocol - Study III

Publishing a study protocol before conducting the trail is a way of securing the quality and validity of the study. Results of the RCT, which was carried out in accordance with the study protocol are discussed below (Study V).

Cognition - Study IV

In this cross-sectional study of primary care patients, anxiety severity was associated with lower EFs related to WM (digit span), in multivariable models, also after adjustment for depressive disorder. In analyses, measuring associations of anxiety severity and cognitive function test scores, we observed associations of anxiety severity with scores on the digit span total (general measure of WM) and backward tests (measuring active WM where information has been switched). No association was found with forward and sequencing tests measuring short-term memory where information is maintained [79] and digit span sequencing, a measure of cognitive flexibility. The results are in line with our hypothesis, indicating a relation between anxiety severity and EFs related to WM.

There is limited literature exploring cross-sectional associations between anxiety disorder and WM. One study investigated WM deficits in patients with GAD and whether these deficits reflect threat-related processes or actual symptoms of the disorder. They found that compared to healthy subjects, individuals with GAD and free from depression, scored lower on WM performance. Further, they found connections to lower prefrontal engagement in patients with GAD suggesting that the cognitive deficits seen in anxiety patients may represent clinical anxiety symptoms and not a consequence of threat [49]. For patients with PD, a meta-analysis found limited support for associations between impairments in short term memory and PD, but no associations between PD and impairments in other cognitive domains such as EF and WM [50].

We did not find an association of anxiety severity and design fluency tests, measuring cognitive flexibility and inhibition. Lower cognitive flexibility (impairments in both episodic memory and executive functioning) have previously been reported for patients with PD with and without comorbid depression, compared to healthy controls, but not for patients with GAD [121]. This could be explained by their small sample size of GAD (n=7), compared to our study population, with a large proportion of patients with GAD (n=107, 57%). Further, one study investigating the effects of GAD on neuropsychological functioning among young adults, compared to healthy controls, indicated that GAD was associated with cognitive impairments, such as attention, non-verbal memory and executive dysfunctions. However, the

observed association suggested a possible effect of antidepressant treatment showing more marked deficits in patients taking antidepressant [122]. We could not show any between-group differences in patients with or without psychotropic medication, measuring cognitive function. However, confounding by indication must be considered as psychotropic medication may influence cognitive function, which may affect the results [123, 124]. Antidepressants have been shown to have positive effects on EF in patients with depression [123], but further research is needed concerning anxiety disorders.

Compared to a normed population our study population scored lower on tests on EFs related to WM and fluid intelligence, in contrast to overall design fluency test where the study population scored higher. An explanation for our results may involve the normative sample for the design fluency test. The D-KEFS normative sample (nationally, U.S., representative, stratified sample, of 1750 nonclinical individuals in ages 8–89 year) used the 2000 U.S. Census figures as target values [125], but cross-national differences in cognitive function exist [126]. U.S. D-KEFS means might be lower than Swedish means. Concerning WAIS-IV test battery they were normed against a Scandinavian population [127]. An additional explanation could be the presence of a "Flynn effect" (the globally observed increase in IQ scores over time) since the making of the D-KEFS normative sample is from year 2000 and our study sample from 2017-2020 [128].

In a large population-based sample of adults the authors could not show a dose-response relationship between anxiety severity, measured as number of comorbid anxiety disorders, and design fluency scores, after adjusting for comorbid depression [129]. However, lower design fluency scores have been shown in patients with comorbid clinical depression and anxiety [130].

Results of a pilot study suggest that EF may predict treatment response to CBT in anxious older adults [131]. Furthermore, research on EF may advance the understanding of the psychopathology of anxiety and identify vulnerability factors. A study from 2018 showed that EF deficits can increase and enhance the association and the impact of repetitive negative thoughts (including worry and rumination found in anxiety and depressive disorders) on the development of anxiety disorder [132]. Understanding executive behavioural control and increasing our knowledge of cognitive function in primary care patients with anxiety disorders is essential, with implications for the development of more individualized treatment strategies, for example CBT, exercise or medication in the future.

Anxiety and intervention 12-week outcome - Study V

This randomized clinical study of primary care patients with anxiety disorders demonstrates that both exercise intensity interventions, improved anxiety symptoms at 12-week follow-up. Improvement in BAI score was independent of depressive symptoms, indicating that the results cannot only be explained by the well-known effect of exercise on patients with depression [26, 133]. The study also supports a significant trend in the fraction of patients with improved anxiety symptoms with increased exercise intensity, but it does not indicate large differences in effect sizes between low and higher intensities. In contrast to a recent review reporting that high intensity exercise interventions were found to be more effective than low intensity interventions for the treatment of anxiety symptoms [57] no clear dose-response effect of exercise intensity was observed in our study. This discrepancy could partly be explained by a large proportion of our study cohort, 50%, living with anxiety for more than 10 years and also being quite unfit at baseline. For these patients, even participation in an exercise program of lower intensity would substantially affect their earlier inactive lifestyle for the better. Moreover, participants in the control group probably also engaged in more physical activity independently, as suggested by the increased cardiovascular fitness for this group, which could suggest underestimated reported effect sizes.

We could not confirm our hypothesis that changes in cardiovascular fitness would predict anxiety outcomes. Only one recent trial has reported a link between changes in maximal oxygen uptake capacity (VO_2max) and clinical symptoms in anxiety disorders [134] and they could not report any relevant correlations between improvements of symptoms and VO_2max changes. Also regarding changes in muscle strength, we and others [135-137] did not find any associations with decreased symptoms of anxiety in persons with anxiety disorders.

Other factors may explain the effects of exercise on anxiety symptoms. The social context and regular meetings with the participants in group exercise could be one explanation for its therapeutic effect. The support from physiotherapist in every exercise session could also explain a part of the symptom reduction for the participants. Further, 27% of the participants in the study were on sick-leave and the routine with three sessions per week, on the same days, may have had a beneficial effect for this group.

Furthermore, research has shown that EF impairments can have a negative effect on repetitive negative thoughts (including worry and rumination) in the development of anxiety and depressive disorder [132].

Understanding the mechanisms behind the recent findings that anxiety could be an independent risk factor for cardiovascular disease [138] highlights the importance of preventive actions. Implementing exercise as a treatment for anxiety disorders in primary care can alleviate anxiety, improve cardiovascular health and might have a great impact both at the individual level and from a societal perspective.

5.2 Strengths and limitations: Study I-II

The Swedish well-validated national registers with comprehensive coverage and almost complete follow-ups, with inclusion of mainly unselected populations and the use of censoring information and missing data, provides a strong base for the examination of associations. A given disease can be caused by more than one causal mechanism, and every causal mechanism involves the collective action of a variety of component causes.

The power of our epidemiological studies is strong considering the large sample size (>1.5 million participants), reducing the possibility of random errors and the broad inclusion limits the risk of patient selection bias [139]. The collection of national registry data is independent of the research question which reduces the risk for bias. Moreover, all data are available from the start and there is no need to wait several years for study outcomes. Furthermore, the economic burden of collecting data for research as in a RCT are not needed. By using the unique personal identification number and adding register-based data from different national registers it is possible to adjust the study outcomes for many potential confounders which increase the specificity.

In Study I, the removal of young men with psychiatric illness before or at conscription, and also three years after, reduced the risk of reverse causation. A major strength of this study was that cardiovascular fitness was objectively measured by bicycle ergometer maximal test, but an important consideration here is that fitness was measured only at baseline, which could be considered a limitation. However, measuring observational data at several points during follow-ups would still not be sufficient for making conclusions about causality. Further, the observational design can also be seen as a general limitation. This design makes it possible to study associations, but we cannot prove causality.

A limitation in Study I is that we were not able to adjust for degree of social functioning at conscription, which might be insufficient in young people who later develop serious mental disorders. Early motor delays in children have been reported as an early sign of schizophrenia [106]. Furthermore, social capability could affect participation in physical activities and the level of cardiovascular fitness at conscription. Long-term intervention studies based on RCT's are needed to increase our understanding of potentially causal

associations, as well as their consistency and possible dose-response relationships.

Limitations in Study II could be that illness duration and symptom severity were not available and could affect mortality outcome. Further, we did not consider episodes of mental disorders that developed after conscription. This is a limitation as comorbidity might increase during the follow-up, thereby affecting mortality risks. We could not analyse any potential associations between symptom ratings and specific causes of death because no data on specific symptoms of depression and anxiety were available. This is a limitation, as early symptoms of anxiety and depression are prospectively related to several main causes of deaths [140]

During the study period the conscription cohort constitute most of the male general population in these age-categories in Sweden. This is a strength because the generalizability to other populations and it is a complete national coverage of Swedish males. A limitation of our data is that results cannot be directly extrapolated to women. Some evidence have shown that physical activity could be more protective in men and this may have impact on our results in Study I [141].

The study outcomes have been adjusted for a variety of potential confounders but still the results could differ in other study context, for example in other countries with different health care systems or ethnic mixes. Other confounders such as substance abuse, might affect both cardiovascular performance at conscription and future psychiatric disorders.

Limitations could be that data not primarily collected for research and thereby all variables of interest might not be available or missing. In longitudinal studies reaching over years or decades, variables relating to for example diagnoses or clinical tests can also have undergone multiple changes.

5.3 Strengths and limitations: Study IV-V

In study V a major strength is the number of participants (n=153), which may be considered large in relation to previous RCT's on exercise as a treatment of anxiety disorders [57, 134, 142, 143]. Further, our adherence rate of 70% was high, considering the long duration (12 weeks) of the intervention and that about one quarter participated during the first wave of the Covid-19 pandemic. Similar or higher adherence rates have been reported for some RCTs using shorter intervention times [134, 143]. Another strength is the comparisons of two different intensities of exercise. We also considered cardiovascular fitness and muscle strength as potential mediators in our statistical analyses. Another strength is that we repeated all analyses and compared the treatment effects in

single-blinded and double-blinded participants group respectively, which did not indicate bias by randomization.

We used the established BAI scale [29] to measure anxiety symptoms since it is often used within Swedish primary care and because it minimizes the risk of depressive content. Although BAI primarily focuses on somatic symptoms, it also captures subjective feelings of anxiety. Our choice of this measure for anxiety symptoms may have influenced the results.

In study IV several limitations are identified. The cross-sectional design makes it impossible to detect causal associations between anxiety severity and EF. There are key gaps in the literature and research regarding the causal link between anxiety disorder and EF. Longitudinal studies will be necessary to investigate this relationship. Deficits in EF can be a consequence of anxiety symptoms but may also increase the development and maintenance of anxiety disorder. Patients with anxiety disorder were also compared to normed populations with regards to cognitive function. However, inclusion of a non-clinical control group instead might have yielded different results. Further, the possibility of selection bias for cognitive functioning cannot be excluded as the study participants were recruited on a voluntary basis. Another factor that might have influenced the test results are in which order the cognitive tests were performed. The test procedure took approximately 35-45 minutes, and the WAIS-IV tests were always performed before the D-KEFS tests and patients with more severe anxiety may have experienced greater fatigue towards the end of the test procedure, compared to patients with milder anxiety. However, the last test was design fluency, which in our analyses showed no association with anxiety severity. Any observed associations could also be affected by variables not measured, influencing both severity of anxiety and cognitive performance.

Moreover, participating in a group-setting, such as the current exercise intervention, may result in improvements due to benefits of interaction with and attention from other people. [53]. In that case a time-matched, active control group exercising individually might have been more appropriate.

The use of self-rating measures is another limitation which increase the risk of an under- or overestimation of symptoms depending on fluctuations in symptoms over time. BAI captures symptoms from the past week but participants may have been influenced by symptoms from the present day. Moreover, even if usage of psychoactive medication was adjusted for, an influence of antidepressants and other psychoactive medication on study outcomes cannot be excluded.

5.4 Diagnostic accuracy

The validity of the diagnosis for schizophrenic disorders and other psychotic disorders in the Swedish National Hospital Discharge Register is high and stable over time [144]. This can be explained by the fact that most persons with these disorders have contact with special psychiatric care at some point in life. All counties in Sweden started to record all psychiatric care and diagnoses, in the Swedish National Hospital Discharge Register in 1973 and forward. Since then the positive predictive values (PPV) for most psychiatric ICD diagnoses are reported to be between 86–99%, but not all mental diagnoses have been individually validated [65]. An important factor is that the incidence is likely to be underestimated for stress-related and somatoform disorders since individuals with these conditions foremost are treated in the primary health care and not in hospitals.

Psychiatric diagnoses identified at conscription through structured examinations and consultations by trained clinicians are a major strength of the epidemiological studies in this thesis. In Study II this method allows identification of men who do not seek healthcare and less severe cases of NPM disorders. Depending on whether men reported symptoms of mental disorders at or prior to conscription during the psychological examination, and therefore referral for further examination by a doctor, may have underestimated our associations. As the number of NPM disorders at conscription decreased over time, there is a possibility that men with more severe mental health issues were excused to a larger extent in later cohorts, which might have had an impact on the associations reported. Due to military confidentiality no information is available to explain the observation of lower prevalence of mental disorders in later cohorts. Possible explanations include changes in how psychiatric disorders were assessed and broader exemption criteria in later-born cohorts.

Documentation of causes of death goes back to the year of 1749 in Sweden [61]. The quality of the cause of death register is affected by several factors. The responsible physician's capability to confirm the cause of death, relies on factors such as the consistency of diagnostic procedures and recording of the death. Studies have evaluated the comparability and validity of the cause of death reported and found that the death certificates often are insufficiently described or do not evaluate the death certificates based on international standards which may affect the generalisability of the conclusions made in epidemiological studies [145]. The availability of an autopsy is also a factor that has to be considered. Overall, the Swedish cause of death register is considered to be of high completeness and due to the long history, data can be utilized over a long period of time. The ability to connect it to several other registers in Sweden is also a major strength. The last check on quality of the Cause of Death Register was made in 2020 by the National Board of Health and Welfare [146].

5.5 Gender aspects

About 25 % of the Swedish population is affected by anxiety disorders at some point in life. Women, both adults and adolescents, are reported to have a threefold increased risk compared to men [24]. An increase in prescribed antidepressants among children and adolescents has been noticed. During time the proportion more pronounced among young females [147]. This increase has been explained by the fact that the proportion of young people with depression and anxiety disorders successively increased over time and not that the disorders are more frequently treated with antidepressants [15].

In 2015, 51 % of women aged 16-29 years reported having symptoms of mental ill-health such as anxiety and worry, compared with 66 % in the year 2020. Corresponding figures for men were 32 % in year 2015 and 42 % in 2020. A similar increase in self-reported mental illness are seen in other countries, with the same difference between females and males [15, 148].

A significant increase in the proportion of adolescent patients treated in psychiatric hospital care was observed in Sweden during the last 10 years, more marked among females 10-24 years of age, see figure 2. This can be explained by several factors. First, there could be an actual increase in need for psychiatric specialist care in hospital in the population. The availability of treatment could also be an explanation. Further, there is a possibility that the society is more aware of mental illness among young people and identify them faster than before. It is difficult to compare the availability of care for different genders in different countries and so is making any conclusion about gender difference and development of incidence in mental illness in other countries.

The epidemiological part of this thesis only included men but in the interventional study both genders were included. However 70% were women, which reflexes the fact that anxiety disorders are more common in women.

5.6 Clinical significance

Anxiety disorders are increasing, especially among young individuals and tend to be lifelong, have poor prognosis and have a high risk for relapse if left untreated [24]. These individuals are at increased risk for future marginalization and elevated morbidity and mortality, which emphasizes the importance of finding and implementing more effective treatment and preventive strategies.

This thesis provides novel insights for exercise as a treatment of anxiety disorders, also in patients with chronic anxiety (> 10 year). We also reported that both low and moderate/high exercise intensity decreased symptoms of anxiety in patients with anxiety disorders. These are all issues that will make it possible to develop optimal exercise protocols, to gain further

comprehension regarding mechanistic aspects, treatment effects and prognosis for clinicians who meet patients with anxiety disorders.

From both a public health perspective and a lifetime perspective for the individual, it is essential to obtain knowledge of how physical activity, cardiovascular fitness and cognitive ability are related over time to psychiatric disorders. Such knowledge will provide a good basis for the society and public health care to make actions for future prevention and intervention. Such a preventive action could be to introduce daily school-based physical activity during all mandatory nine years and in high-school in Sweden to reach and provide a daily based routine for physical activity in young people. Also, prescription of physical activity in health care by professionals can be expanded. Furthermore, the infrastructure could be made more accessible for bicycles and walking and the environment be planned to better facilitate physical activity such as attractive schoolyards and playgrounds for children and young people. For the health care it is important to make youth clinics more accessible with available professionals to take care of the growing numbers of young people with mental illness.

For primary health care it is essential to find treatments that are easy to perform, have minimal side-effects and are possible to implement in clinical practice. It is important, not only for the patients but also for the society and the primary healthcare organization, stakeholders and regional politicians to find solutions for reducing medical and sick-leave costs.

5.7 Utilization and communication of research results

We have with this thesis reported new knowledge concerning cardiovascular fitness as a risk factor for mental disorder, non-psychotic mental disorder as a risk factor for premature death and cause-specific mortality and that severity of anxiety symptoms are related to decreased executive functions related to working memory. Furthermore, we have communicated our results that cardiorespiratory and resistance exercise, of both low- and high intensity exercise, for patients with anxiety disorder within primary care can reduce symptoms of both anxiety and depression.

To report our results to clinicians, in addition to presenting our results in academic international journals, we have presented our results from Study II at an international academic conference visited by health professionals (EPA Gothenburg 2016). After a press release with results from Study V we were able to communicate our results in several media channels as public radio[1], international radio[2], Swedish television[3], newspapers[4] and online publication[5]. We were quoted by media for example in India, USA, United Kingdom, Australia and Spain. We have been aware of that these results attract attention worldwide from a large number of individuals and media, acknowledging it as

an important issue for many people and media who wants to find preventive methods and treatment for anxiety symptoms.

It is important acknowledging the third Sustainable Development Goal set by the United Nations General Assembly in which it is stated that noncommunicable diseases such as mental disorders as well as well-being should be prioritized and reduced up to year 2030. These efforts may reduce the somatic and mental burden later in life for many people.

[1]*P4 Radio Halland, November 9, 2021*
[2]*Radio Sweden, Sveriges Radio's English service*
[3]*TV4 Nyheter, November 9, 2021; TV4 Morgon, November 10, 2021*
[4]*Dagens nyheter. November 10, 2021, https://www.dn.se/sverige/svensk-studie-traning-lindrar-langvarig-angest-patagligt-forbattrade/; Aftonbladet; Expressen; Idrottsmedicin; Dagens ETC; Läkemedelsvärlden, November 11, 2021; Dagens medicin, November, 2021; Special Nest, December, 2021; Dagbladet (Norway); December, 2021*
[5] *Health Europa Quarterly, Issue 20, 2021; Elemental, November 12, 2021 https://robertroybritt.medium.com/the-ultimate-anxiety-buster-exercise-9e3afbb84d55; Mediehuset Bergens Tidende, November, 2021, https://www.bt.no/sprek/; Hearst Lifestyle Group, December, 2021; NBC News in the U.S., January, 2022; Daily Mail in the UK, December, 2021, https://www.dailymail.co.uk/sciencetech/article-10352711/Anxiety-effectively-treated-exercise-study-finds.html; Inverse, January, 2022, https://www.inverse.com/mind-body/exercise-anxiety*

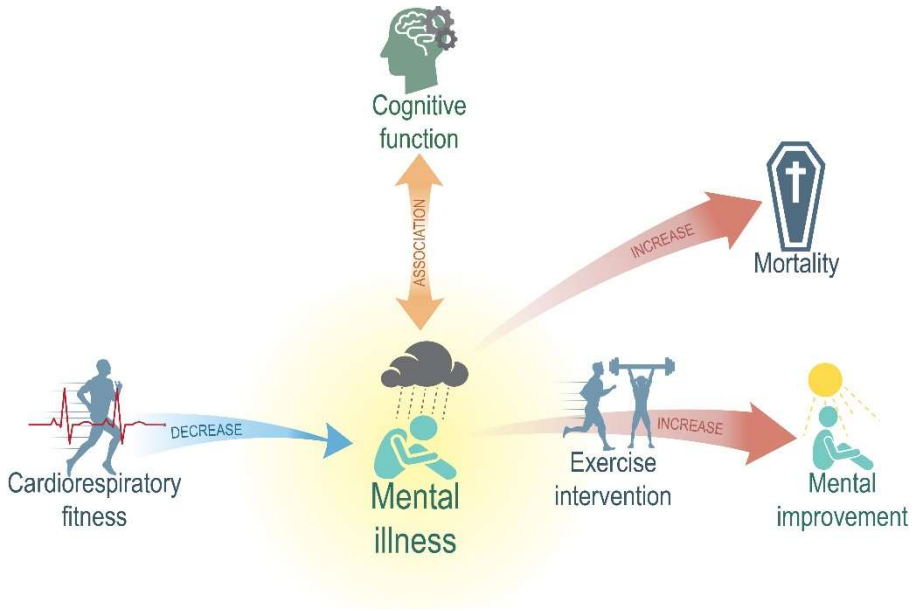

Figure 8. Conclusions. With permission from Jenny Nyberg,2022.

6 CONCLUSION

General conclusions

Since anxiety disorders are common and rising in prevalence, it is important to find preventive actions and affordable treatment. These findings contribute with knowledge that physical exercise represents an effective treatment and should be made available in clinical practice for persons with anxiety issues within primary care. See figure 8 for an overview of conclusions.

Specific conclusions

1. Lower cardiovascular fitness in late adolescent males is associated with increased risk of serious non-affective mental disorders in adulthood, also after adjusting for familial influences.

2. Young men diagnosed with NPM disorders have a long-term increased mortality risk, in particular due to infectious and gastrointestinal conditions.

3. Severity of anxiety among individuals with anxiety disorder within primary care was associated with executive functions related to working memory.

4. A 12-week guided exercise intervention within primary care for patients with anxiety disorders was associated with reduced symptoms of anxiety, irrespective of exercise intensity.

7 FUTURE PERSPECTIVES

Every third patient in the waiting room at a Swedish healthcare center is seeking help for mental problems, including anxiety disorders. In Sweden anxiety disorders are increasing, especially amongst young women. This thesis provides new knowledge in potential risk factors, such as cardiovascular fitness, in young age for future risk of psychiatric disorders as well as for the risk of cause-specific mortality among young men with NPM disorders. Well-controlled, prospective studies are needed to investigate modifiable risk factors across anxiety disorders. Addressing the increased risk in mortality for individuals with NPM disorders in future research is needed to ascertain early preventive efforts aimed at reducing the increased mortality risk and associated somatic morbidities. Potential increased mortality risks should also be explored in women. Further, this thesis contributes with new findings for effective treatment and provides new directions for prevention and treatment for patients with anxiety disorders in primary health care. Since our findings indicate that exercise can be an alternative treatment and could be beneficial for patients with anxiety disorders in primary health care, forthcoming studies could address the use of guided exercise in separate categories of anxiety disorders and also compare effects of exercise on anxiety symptoms for acute and chronic conditions.

Our findings that severity of anxiety among patients with anxiety disorder in primary care contexts was negatively associated with EF related to WM, has implications for the understanding of executive behavioural control in primary care patients with anxiety disorders. Finding more individualised treatments to improve cognitive functions and anxiety symptoms are essential and missing today. To achieve this, we have to characterise cognitive functions and find interventions to improve specific cognitive domains when needed. Research on EF may identify vulnerability factors and explain more of the psychopathology of anxiety.

The consequences of different forms of mental illness have a large impact on the society and the national economy. In Sweden these issues are prioritised and a huge challenge for the future. Due to the increasing prevalence of mental illnesses, the government in Sweden the last five years collaborated with the Swedish Association of Local Authorities and Regions (SALAR) and the National Board of Health and Welfare in over 70 different projects concerning these issues [15].

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