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BURNOUT AND SICK LEAVE DUE TO MENTAL DISORDERS: HERITABILITY, COMORBIDITY, RISK FACTORS AND ADVERSE OUTCOMES

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Stockholm 2017

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Printed by E-Print AB 2017
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ISBN 978-91-7676-843-3

BURNOUT AND SICK LEAVE DUE TO MENTAL DISORDERS: HERITABILITY, COMORBIDITY, RISK FACTORS AND ADVERSE OUTCOMES

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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“I am of certain convinced that the greatest heroes are those who do their duty in the daily grind of domestic affairs whilst the world whirls as a maddening dreidel”.

Florence Nightingale

ABSTRACT

Common mental disorders are an increasing public health problem worldwide, and in Sweden the incidence of sick leave due to stress-related mental disorders has more than doubled since 2010. The aim of this thesis was to explore genetic and environmental aspects of burnout and sick leave due to stress-related and other mental disorders. Data from the population based Swedish Twin Registry's questionnaire study STAGE (the Study of Twin Adults Genes and Environment) and population registers, including the MiDAS (MicroData for Analyses of the Social insurance) register, were used.

Study I was cross-sectional and included 25 378 twins that responded to STAGE. A multivariate biometric twin model was used to assess to what degree the covariation between major depressive disorder, generalized anxiety disorder, and burnout, was explained by common genetic and environmental factors in women and men. A latent common factor explained that the covariation was influenced 58% by genetics and 42% by unique environment.

Studies II-III were prospective and contained 23 611 and 11 729 STAGE responders respectively. Information from the MiDAS register was used to follow up for sick leave. In Study II logistic regression with co-twin control and a bivariate twin model was used to assess whether the associations between burnout and sick leave due to stress-related mental disorders, other mental disorders, and somatic conditions, was influenced by familial factors (genetics and shared environment). The phenotypic correlation between burnout and sick leave due to stress-related mental disorders (0.26), and between burnout and sick leave due to other mental disorders (0.30) was explained by genetic factors. The association between burnout and sick leave due to somatic conditions was modest and not influenced by familial factors. In Study III, logistic regression models were used to assess whether psychosocial work environment and health behaviors were risk factors for sick leave due to mental disorders and if the associations were influenced by familial factors. Job strain was a risk factor for sick leave due to mental disorders, after controlling for familial factors, while none of the health behaviors showed independent associations with sick leave due to mental disorders.

Study IV was register based and contained 2202 individuals on sick leave due to a mental disorder 2005-2006, according to MiDAS, and their 2202 co-twins. Cox proportional hazards regression models with co-twin control was used to investigate the short and long term effect of sick leave due to mental disorders on the outcomes reoccurring sick leave, disability pension, and unemployment, while taking familial factors into account. The risk of reoccurring sick leave was more than 3 times higher for the first two years of follow up. The risk of disability pension was 12 times higher the first year and remained almost 3 times higher throughout the rest of the follow-up time. The twice as high risk for long-term unemployment was consistent over the up to 8-year follow-up time.

In conclusion, burnout shares a genetic vulnerability with depression, anxiety, and sick leave due to mental disorders. Job strain is a risk factor for sick leave due to mental disorders regardless of familial predisposition. Sick leave due to mental disorders is a public health problem that may have serious consequences, both for individuals and to society as a whole.

SVENSK SAMMANFATTNING

Psykiska sjukdomar är ett ökande folkhälsoproblem över hela världen, och i Sverige har incidensen av sjukskrivningsfall i anpassningsstörningar och reaktioner på svår stress mer än fördubblats sedan 2010. Syftet med den här avhandlingen var att undersöka genetiska och miljömässiga aspekter av utmattning och sjukskrivning i psykiska diagnoser. Data från en enkätstudie (STAGE) genomförd av det svenska tvillingregistret och nationella register inklusive MiDAS (MicroData för Analys av Socialförsäkringen) användes.

Studie I var en tvärsnittsstudie som inkluderade 25 378 tvillingar som svarat på STAGE. En multivariabel biometrisk tvillingmodell användes för att bedöma i vilken grad depression, generaliserat ångestsyndrom, och utmattning förklarades av gemensamma genetiska och miljömässiga faktorer hos kvinnor och män. En modell med gemensam underliggande faktor passade data bäst och den gemensamma faktorn som förklarade samvariationen påverkades till 58 % av genetik och 42 % av unik miljö.

Studierna II-III var prospektiva studier och inkluderade i 23 611 respektive 11 729 tvillingar som svarat på STAGE. Information från MiDAS-registret användes för att följa upp för sjukskrivningar. I Studie II användes logistisk regression och en bivariat tvillingmodell för att bedöma huruvida sambandet mellan utmattning och sjukskrivning på grund av stressrelaterade, andra psykiska diagnoser, och somatiska diagnoser påverkades av familjära faktorer (genetik och delad miljö). Korrelationen mellan utmattning och sjukskrivning på grund av stressrelaterade psykiska diagnoser (0,26) och mellan utmattning och sjukskrivning på grund av andra psykiska diagnoser (0,30) förklarades av genetiska faktorer. Sambandet mellan utmattning och sjukskrivning på grund av somatiska diagnoser var svagt och påverkades inte av familjära faktorer. I Studie III användes logistiska regressionsmodeller för att undersöka om psykosocial arbetsmiljö och hälsorelaterade beteenden var riskfaktorer för sjukskrivning i psykiska diagnoser och om sambanden påverkades av familjära faktorer. Spänt arbete var en riskfaktor för sjukskrivning i psykiska diagnoser, efter att ha kontrollerat för familjära faktorer, medan inget hälsorelaterat beteende visade samband med sjukskrivning på grund av psykiska diagnoser efter kontroll för familjära och andra faktorer.

Studie IV var registerbaserad och inkluderade 2202 personer som var sjukskrivna på grund av en psykisk diagnos 2005-2006, enligt MiDAS, och deras 2202 tvillingsyskon. Cox regressions modeller användes för att undersöka den kort- och långsiktiga effekten av sjukskrivning i psykiska diagnoser på utfallen upprepade sjukskrivningsfall, sjuk- eller aktivitetsersättning och arbetslöshet, justerat för familjära faktorer. Risken för upprepade sjukskrivningsfall var mer än 3 gånger högre de två första åren av uppföljningen. Risken för sjuk- eller aktivitetersättning var 12 gånger högre det första året, och nästan 3 gånger högre under resten av uppföljningstiden. Den dubbelt så höga risken för långtidsarbetslöshet var stabil under den upp till 8 åriga uppföljningstiden.

Sammanfattningsvis, utmattning delar en genetisk sårbarhet med depression, ångest och sjukskrivning i psykiska diagnoser. Spänt arbete är en riskfaktor för sjukskrivning på grund av psykiska diagnoser, oavsett familjär predisposition. Sjukfrånvaro på grund av psykiska diagnoser är ett folkhälsoproblem som kan få allvarliga konsekvenser, både för individer och för samhället som helhet.

LIST OF SCIENTIFIC PAPERS

I. Mather L, Blom V, Bergström G, Svedberg P. An Underlying Common Factor, Influenced by Genetics and Unique Environment, Explains the Covariation Between Major Depressive Disorder, Generalized Anxiety Disorder, and Burnout: A Swedish Twin Study. Twin Research and Human Genetics. 2016; 9(6): 619-627.

II. Mather L, Bergström G, Blom V, Svedberg P. The Covariation Between Burnout and Sick Leave Due to Mental Disorders Is Explained by a Shared Genetic Liability: A Prospective Swedish Twin Study With a Five-Year Follow-up. Twin Research and Human Genetics. 2014; 17(6): 535-44.

III. Mather L, Bergström G, Blom V, Svedberg P. High Job Demands, Job Strain, and Iso-Strain Are Risk Factors for Sick Leave due to Mental Disorders: A Prospective Swedish Twin Study With a 5-Year Follow-Up. Journal of Occupational and Environmental Medicine. 2015; 57(8): 858-65.

IV. Mather L, Blom V, Bergström G, Svedberg P. Adverse outcomes of sick leave due to mental disorders: a prospective study of discordant twin pairs. Scandinavian Journal of Public Health. 2017. [Epub ahead of print] doi:10.1177/1403494817735755

CONTENTS

LIST OF ABBREVIATIONS

ICD	International Statistical Classification of Diseases and Related Health Problems
DSM	Diagnostic and Statistical Manual of Mental Disorders
DNA	Deoxyribonucleic acid
RNA	Ribonucleic acid
STODS	Swedish Twin project Of Disability pension and Sickness absence
STAGE	The Study of Twin Adults Genes and Environment
STR	The Swedish Twin Registry
MiDAS	MicroData for Analyses of the Social insurance
LISA	Longitudinal integration database for health, insurance and labor market studies register
A	Additive genetic influences
D	Non-additive genetic influences
C	Shared environmental influences
E	Unique environmental influences
CI	Confidence Interval
OR	Odds ratio
HR	Hazard ratio
PBSE	Performance-based self esteem

1 INTRODUCTION

While the health of the Swedish population is generally improving, the prevalence of the common mental disorders depression, anxiety, and stress-related disorders are increasing in women and men of all age groups (1). The increase is reflected in sick-leave rates, sick leave has increased between 2010 and 2015, and in particular the incidence of sick leave due to stress-related mental disorders (adjustment disorders and reaction to severe stress), more than doubled during this time (2). These disorders are also increasing worldwide (3) and mental disorders are one of the most common reasons for work disability in Europe (4). The common mental disorders are complex traits whose development involve many genes and environmental factors (5). Moreover, aspects other than mental disorders such as work-related factors, health status, socio-economic situation and family background, are of importance when studying sick leave (2, 6-9). How sick leave affects an individual varies depending on life situation (10), but on population level, sick leave due to mental disorders has been found to increase the risk of future absence from the labor market in forms of further sick leave, disability pension, and unemployment (11), causing high costs and lower productivity for society (12, 13). In order to address this major public health problem, more knowledge is needed on how these common stress-related and other mental disorders develop, how they lead to sick leave and what consequences this may have.

In this thesis, self-reported levels of burnout, measured with the Pines Burnout Measure, as well as sick leave due to stress-related and other mental disorders, were studied in a population of twins. Studying twins enabled us to examine the variability of these measures more closely in the population, in terms of genetics and environment shared by the twin pairs and environment unique to each twin. The focus was on how genetics and shared environment influenced the covariation between burnout, mental disorders and sick leave, as well as studying environmental risk factors and outcomes that were independent of these factors.

1.1 STRESS AND MENTAL HEALTH

Even though stress is understood when used in everyday language, there is no agreed upon definition of stress (14), instead, the term is used to describe a wide range of both stimuli and responses (15). The term stress as it is used today was introduced by Hans Selye in the 1930s. He defined stress as “The nonspecific response of the body to any demand made on it” (16, p.32) and he later described the response of the body to the stress as the general adaptation syndrome, with three stages: alarm, resistance and exhaustion (17). Lazarus and Folkman later developed a theory where they focused on the relationship between the individual and environment. In order for an external organism to cause illness, the person also needs to be susceptible. In other words, psychological stress depends to a large extent on an individual’s cognitive appraisal of the stressor (15). Mental health is defined by the World Health Organization as “a state of well-being in which every individual realizes his or her own potential, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to her or his community” (18).

1.2 CONCEPTUAL FRAMEWORK

1.2.1 Burnout and exhaustion disorder

Burnout, like stress, lacks an agreed upon definition (19). The term is thought to originate from the fictional book "A burnt out case" from 1961. In the book an architect´s stress-related health problems is compared to that of end stage leprosy, where the patients are cured, but missing limbs, and are suffering from the psychological consequences of the disease i.e., "burnout" (20). Burnout started appearing in the scientific literature in the 1970s in publications by Freudenberger (21), a psychiatrist and Maslach (22), a social psychologist. Maslash describes burnout as having three dimensions: exhaustion, cynicism, and a sense of ineffectiveness. Maslach defined burnout as a work related phenomenon in the caring professions that focused on the relationship between the staff and client (23). In the 1980s the Maslash Burnout Inventory, was developed, that remains the most common measure of burnout (24). At a similar time Pines developed a measure that takes a wider perspective on burnout and could be used also in non-working populations, the Pines Burnout Measure (25). Pines describes burnout as a condition caused by long-term stress, characterized mainly by emotional exhaustion (25). The Pines Burnout Measure, the measure of burnout used in this thesis, correlates mainly with the exhaustion dimension of the Maslash Burnout Inventory (26).

Previous studies have found that burnout has an effect on physical health (27-29) and it often co-occurs with mental disorders such as depression (30) and anxiety (31, 32). In addition to being prevalent in "people working with people" (23), high levels of burnout has been found among students (33), athletes (34), family caregivers (35-37) as well as those unemployed (38). Well known risk factors for burnout include a poor psychosocial work environment (23, 39, 40). Personality traits such as neuroticism (23) and performance based self-esteem (41, 42) has also been studied in relation to burnout, however to a lesser extent.

Socio-demographics that have been studied in relation to burnout include sex, age and socioeconomic status. Internationally there are no large sex differences in burnout (43), however, in Sweden burnout is more prevalent among women (38, 44). Burnout is usually found to decrease with age in the studies that have been based on working populations (45). However, little is known about whether burnout really declines with age, or whether it is rather the case that those with burnout exit the workforce early i.e., the healthy worker effect. A population based study from Sweden found the association between burnout and age to be weak (38). The association between burnout and socioeconomic status is unclear. Some studies have found burnout is more common among those with higher education (23), while Swedish studies have found that burnout is more common among women blue collar workers (44, 46), and another study found no association (38).

Because burnout has been traditionally studied in working populations, there are fewer studies investigating clinical burnout i.e., when the burnout has become so severe that the person can no longer work and needs professional help (47). However, previous research has

found that burnout is a risk factor for sick leave due to mental disorders (48, 49). Long-term sick leave due to stress and mental disorders has increased since the 1990s in Sweden, and as a response, the National Board for Health and Welfare appointed a working group, with a task of developing a basis on how these stress-related disorders was to be examined, diagnosed, treated and rehabilitated. As a result the diagnosis "Exhaustion disorder", sometimes also referred to as clinical burnout, was added to the ICD (International Statistical Classification of Diseases and Related Health Problems) 10 under the heading F43 "adjustment disorders and reaction to severe stress" in 2005 (50). Also included in the F43 heading "Adjustment disorders and reaction to severe stress" are acute stress reaction, post-traumatic stress disorder, adjustment disorder, other reactions to severe stress than exhaustion disorder and unspecified reactions to severe stress (50). The diagnostic criteria for exhaustion disorder can be found in Table 1. As well as often co-occurring with other mental disorders, somatic symptoms in patients with stress-related mental disorders are also very common (51).

1.2.2 Depression and anxiety

Depression and anxiety are major public health problems worldwide and have contributed to the increase of years lived with disability (3). There is a treatment gap and many meeting the criteria for these disorders have been found to not have had any treatment for their mental health problems (52-54). The lifetime prevalence of major depressive disorder has been found to be 13-16% in Europe and the United States, while the lifetime prevalence of generalized anxiety disorder was found to be 3% (53, 55). In Sweden 2009 the point prevalence was found to be 5.2% (95% CI: 4.0–6.5) for major depressive disorder and 8.8% (95% CI: 7.3–10.4) for generalized anxiety disorder in a sample representative of the general population (52). Comorbidity between depression and anxiety is common (52, 53), and in those with comorbid disorders, the disorders are generally more severe (52, 56). Depression and anxiety can be found in both ICD and DSM (Diagnostic and Statistical Manual of Mental Disorders) and the criteria are very similar (57, 58). Diagnostic criteria for major depressive disorder and generalized anxiety disorder according to DSM-IV can be found in Table 1.

1.2.3 Sick leave due to stress-related and other mental disorders

Since 2014 mental diagnoses are the most common reason for sick leave reimbursed by the Social Insurance Agency in Sweden (2). Moreover, mental diagnoses represents the longest sick-leave duration, the lowest rates of return to work, and highest risk of disability pension (59). Among the mental disorders, the most common sick-leave diagnoses are stress-related mental disorders, depression, and anxiety disorders. Comorbidity between these mental disorders is common (60) and a study found that 85% of those on sick leave due to a stress-related disorder also fulfilled the diagnostic criteria for depression (61). Sick leave due to mental disorders are more common in the middle age groups and among women (62). In fact, the gender differences are larger in sick leave due to mental disorders than in sick leave in general, and of those on sick leave due to stress-related mental disorders 75% are women (63). In a questionnaire study of those on long term sick leave, those with a mental diagnoses reported more both positive and negative consequences of their sick leave, compared to other

diagnoses groups (10). It should be noted that even though sick leave due to mental disorders is common, many of those with symptoms of mental disorders are not on sick leave (64). About 2 % of the working-age population was on sick leave due to a mental disorder 2012, while 21% of women and 15% of men reports having poor mental health in the national public health survey 2013 (64). Hence, sick leave is not a measure of the disease itself, but rather a measure of the social consequences of the disease in terms of work incapacity (6).

1.2.4 Summary of diagnostic criteria for major depressive disorder, generalized anxiety disorder, and exhaustion disorder

Table 1 contains a summary of the diagnostic criteria for major depressive disorder and generalized anxiety disorder according to the DSM-IV (57) and exhaustion disorder according to the Swedish version of ICD-10 (50). Exhaustion disorder is classified under F43 (adjustment disorders and reaction to severe stress). Burnout was measured in this thesis with the Pines Burnout Measure, which is a self-report scale of burnout symptoms, and therefore does not have diagnostic criteria.

Table 1: Diagnostic criteria for Major depressive disorder and Generalized anxiety disorder as per DSM-IV and exhaustion disorder as per ICD-10.

Major depressive disorder	**Generalized anxiety disorder**	**Exhaustion disorder**
A. Five of the following symptoms during the same 2-week period with at least one of the symptoms 1 or 2 C. Cause clinically significant distress or impairment in social, occupational, or other important areas of functioning, E. Not be better accounted for by bereavement	A. Excessive anxiety and worry, occurring more days than not for at least 6 months C. About a number of events or activities, associated with three or more of the following	A. Physical and psychological symptoms of fatigue for at least two weeks that have developed as a result of one or more identifiable stressors which have persisted for at least six months must be present B. A substantial lack of mental energy dominates the picture, which shows itself in reduced enterprise, decreased stamina or prolonged recovery in associated with psychological stress C. At least four of the following symptoms have persisted virtually every day during the same two-week period
1. Depressed mood most of the day, nearly every day 2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day 3. Significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day 4. Insomnia or hypersomnia nearly every day 5. Psychomotor agitation or retardation nearly every day 6. Fatigue or loss of energy nearly every day 7. Feelings of worthlessness or excessive or inappropriate guilt nearly every day 8. Diminished ability to think or concentrate, or indecisiveness, nearly every day 9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide	1. Restlessness or feeling keyed up or on edge 2. Being easily fatigued 3. Difficulty concentrating or mind going blank 4. Irritability 5. Muscle tension 6. Sleep disturbance	1. Difficulty concentrating or memory impairment 2. Significantly reduced ability to manage claims or to do things under time pressure 3.Emotional lability and irritability 4. Sleep disturbance 5. Substantial bodily weakness or fatigue 6. Physical symptoms such as pain, chest pain, palpitations, gastrointestinal symptoms, dizziness and sound sensitivity. 7. The symptoms cause clinically significant distress or impairment in social, occupational or other important areas 8. The symptoms are not due to the direct physiological effects of a substance (eg, a drug of abuse, medication) or a general medical condition / injury (eg hypothyroidism, diabetes, infectious disease) 9. If the criteria for major depression, dysthymia and generalized anxiety disorder simultaneous fulfillment of specified fatigue syndrome only as additional specification to the current diagnosis

1.3 SOCIAL INSURANCE IN SWEDEN

1.3.1 Sick leave

In Sweden, everyone above 16 years old with an income from work, unemployment benefit, or parental leave, that is unable to work due to disabilities, illnesses, or occupational injuries can apply for sickness benefit. After a qualifying day, the employer pays up to 80% of the worker's wage in sick pay for the first two weeks, after which the Social Insurance Agency takes over (65). A medical certificate is required from day 8 of sick leave. Those who are unemployed, self-employed, or on parental leave apply for sickness benefit directly to the Social Insurance Agency. Sick-leave benefit can be granted full time, 75%, 50%, or 25%, of regular work hours depending on the reduction in work capacity (65).

Long-term sick-leave rates are high in Sweden and interventions to reduce the length of sick leave have been implemented by the government. In 2008 recommendations on sick-leave duration for specific diagnoses, and time limits were introduced (66). Since the changes, after 90 days of sick leave, an individual is only granted further sick leave if they are not able to perform any duties at their place of employment, and after 180 days, any duties on the entire job market (66). Sick-leave rates are currently rising after being reduced between 2002 and 2010 (67) and are highest among healthcare workers, which are also the largest group of employees, representing 13% of the workforce (67). Sick-leave rates are twice as high among women compared to men, and higher in older workers compared to younger (67). Sick leave is more common among groups with lower socioeconomic status (66), however, sick-leave rates are now increasing in professions requiring higher education (67). Negative outcomes of being on sick leave that have previously been studied include premature death (68), suicide (69), reoccurring sick-leave (70), disability pension (71), unemployment (11, 12), low income (72), and poor physical and mental health (73). The effect of sick leave can vary depending on gender, education and immigration status (11, 74), as well as age and diagnosis (10). In order to facilitate comparison between sick-leave studies, they can be categorized in the structure shown in Table 2, and perspectives taken in this thesis are marked in bold (75).

Table 2: Categorization of studies of sickness absence, perspectives taken in this thesis has been marked in bold.					
What is studied?	-Design -Studied -Data -Analyses	Scientific discipline	-Perspective taken in the research questions -Studied	Structural level of the factors included in the analyses	Diagnoses
1. Factors that hinder or promote sickness absence/disability pension 2. Factors that hinder or promote return to work **3. Consequences of being on sickness absence/disability pension** 4. Sickness certification practice 5. Methods, theories	*Study design* **-Cross sectional** **-Longitudinal** -RCT, CT *Type of data* Interview **Questionnaire** **Register** Medical files Insurance files Notes Documents Video Other *Type of analyses* - Qualitative -**Quantitative**	Economy Law Management Medicine **Psychology** Sociology **Public health** **Epidemiology** Philosophy **Behavioral genetics**	*Perspective* That of the: **-Society** -Insurance -Healthcare -Employer -Family -Patient *Studied* **General population** **Twins** Insured **In paid work** (**general** or special jobs/organizations) Diagnosed **Sickness absent**	-National -Local -Worksite -Health care -Family **-Individual**	**All** **Mental** Musculoskel. Cancer MS Hearing CVD Infections Injuries Diabetes Etc.

1.3.2 Disability pension

If the work capacity is long term or permanently reduced, the individual can apply for disability pension which covers up to 64% of lost income (65). Disability pension is given to those 30-64 years old who will probably be unable to work full-time again for the foreseeable future, and those 19-29 years old who will probably be unable to work full-time for at least a year. As sick leave it can be given 100%, 75%, 50%, or 25%, of regular working hours.

1.3.3 Unemployment benefits

Unemployment benefits are covered by sector-specific unemployment benefit funds, requiring membership, covering up to 80% of lost income. There is also a basic insurance for those who are over 20 years old and not a member of such fund, with a compensation rate of 8000 Swedish kronor per month. Unemployment benefit can be given up to 450 days and no payment is given in the first week of unemployment. In order to qualify for benefits an individual must register as a job seeker at the Swedish National Employment Office and be at the "disposal of the job market" i.e., be fit to work at least 3 hours per day and an average of 17 hours per week (76).

1.4 WORK, HEALTH BEHAVIOURS, AND MENTAL HEALTH

Being employed is generally good for mental health and provides positive effects in many aspects of life, such as financial security, social identity and contacts, a sense of purpose and making a contribution to the community, as well as providing activity and a time structure (77). Unemployed individuals have been found to have lower psychological and physical well-being than those employed (78). Hence, returning to work as soon as possible is seen as desirable for people sickness absent due to common mental disorders and many interventions have been developed to enhance return to work (79). Long sick-leave spells are usually seen as detrimental to health and early part-time return to work has been found to be beneficial (66), also for those on sick leave due to mental disorders (80). In a randomized study of those with sick leave due to musculoskeletal disorders, early part-time return to work was found to both reduce the duration of the sick-leave spell, and also improve self-rated health and health-related quality of life (81, 82). Burnout may also be negatively affected by long absences from the job market, as burnout has been found to be twice as high in those unemployed than in those in paid work (38). Moreover, risk of unemployment and a perceived worsening financial situation have been found to increase levels of burnout in a prospective study (83).

However, the work environment can also affect health in negative ways (84). In Sweden, since the beginning of the 1980s, an increasing share of employed people have reported their work is hectic and mentally taxing (9). Hence, in cases where the work environment is unhealthy, measures need to be taken before returning to work for those on sick leave. A common measure of the psychosocial work environment is the job demand-control-support model developed by Theorell and Karasek (85). The basis of this model is that job demands that are too high in combination with low control over one's work situation are detrimental to health. A third aspect of low social support in the workplace, was later added to the measure (86). Burnout was initially described as a result of job stressors (23). Hence, there are many studies that have linked a poor psychosocial work environment to burnout (39, 87). Moreover, studies have also found that a poor psychosocial work environment is a risk factor for sick leave (88, 89). Even though the individuals health is important for returning to work, the workplace need to be involved if return to work after sick leave due to mental disorders is going to be successful (64). Relatively low demands and high control have been found to be associated with return to work (90) and workplace-oriented rehabilitation measures and changing occupation have been shown to reduce the odds of further sick leave in those who had been sickness absent due to mental disorders (91).

People experiencing work strain have been found to be more likely to have an unhealthy lifestyle, compared with those who do not, in terms of smoking, alcohol intake, and leisure-time physical activity (92). Poor self-care in form of adverse health behaviors including smoking, excessive alcohol use and a lack of physical activity has been found to be risk factors for sick leave (93-97). There is also an excess mortality among psychiatric patients (98, 99) and having sick leave due to a mental disorder has been found to be a risk factor for premature mortality (68, 100), a possible contribution to this is adverse health behaviors. Burnout has been found to affect physical health, in that it increases the risk for diabetes,

cardiovascular disease, and predicts mortality (27-29), however, there are only few studies (47).

1.5 GENETICS AND HERITABILITY

The human genome is the complete DNA (deoxyribonucleic acid) content of an individual and consists of 3 million base pairs organized on 23 chromosomes. A gene refers to the section of DNA that encodes a functional product such as a protein or RNA (ribonucleic acid), the human genome contains approximately 25 000 genes. In 2003, the mapping out of the entire human genome was completed (5). Humans share 99.9% of their genome; about 1 in 1000 bases differs between individuals, and these differences make the human genome unique to each individual, the exception being monozygotic (identical) twins (5). These different variants are known as alleles, and each genetic locus consists of two alleles, one which is inherited from the mother and one from the father. Hence the probability that two full siblings will share a specific allele is 50% and therefore we say that full siblings share approximately 50% of their segregating genetic material. The probability that siblings share both alleles at a location is 25% (50%*50%) (5). Twin studies take advantage of the fact that identical, also called monozygotic twins come from one fertilized egg, while fraternal, also called dizygotic twins come from two separately fertilized eggs. This means that monozygotic twins are expected to be genetically identical, while dizygotic twins are as genetically similar as regular full siblings, while both types share environment growing up to the same extent (if raised together). Monozygotic twins are almost always the same sex (except in some very rare cases (101)) and dizygotic twins can be either same or opposite sex (5).

In twin research the known genetic relationships between twins is used to estimate the contribution of genes on a trait, the covariation between two or more traits, and this is referred to as heritability (102). Moreover, using the twin siblings as a reference in a matched analysis and hence adjusting for all factors shared by the twins in a pair (familial factors) is possible. Since heritability studies are based on the known genetic relationships, the genes are unmeasured and no specific genes are identified (103).

Heritability is population specific i.e., is explaining the proportion of the variance in the measured sample that is explained by genetic factors and this may differ between populations and time points. Heritability can differ between sexes and early and late in life and is dependent on the environment. If the environment is exactly equal for all in a population heritability will be 100% i.e., genetics will explain all the variation and if there is a lot of environmental variation, heritability will be lower (102). Certain diseases are caused by a single gene, such as Huntington’s disease, however, for complex traits such as the common mental disorders, many genes are involved as well as many environmental factors (5).

1.5.1 Twin studies of stress, mental health, and sick leave

Meta-analyses of twin studies have found that depression and anxiety are moderately heritable (104, 105), and two twin studies have found that burnout seems likewise heritable (106, 107). Moreover, sick leave and disability pension, both in general and due to mental disorders, have also been found to be heritable (7, 108-110). In a twin study of disability pension due to mental disorders, a third of the heritability overlapped with the heritability for major depressive disorder and generalized anxiety disorder. Hence, many other genetic and environmental factors were involved in explaining the variation (111). In another twin study the association between depression, anxiety, and sick leave due to mental disorders was explained by both genetic and unique environmental factors (112). Hence, the heritability of sick leave does not seem to be only influenced by the fact that the underlying disorder is heritable. Twin studies of risk factors for sick leave and disability pension due to mental disorders have found that high job demands, occupational group, self-rated health and health behaviors seem to be risk factors for disability pension due to mental disorders independent of familial factors (113, 114). On the other hand, the association between socio-economic status and sick leave due to mental disorders seem to be explained by familial factors in young adults (115). Moreover, a twin study found that genetic factors seem to be involved in the transition from long-term sick leave to disability pension (110). Since there are only few studies, further studies on risk factors and adverse outcomes of sick leave due to mental disorders taking genetics and shared environment into account are needed, as well as studies more closely examining the heritability of such sick leave. In Figure 1, an overview of the studies in this thesis is provided.

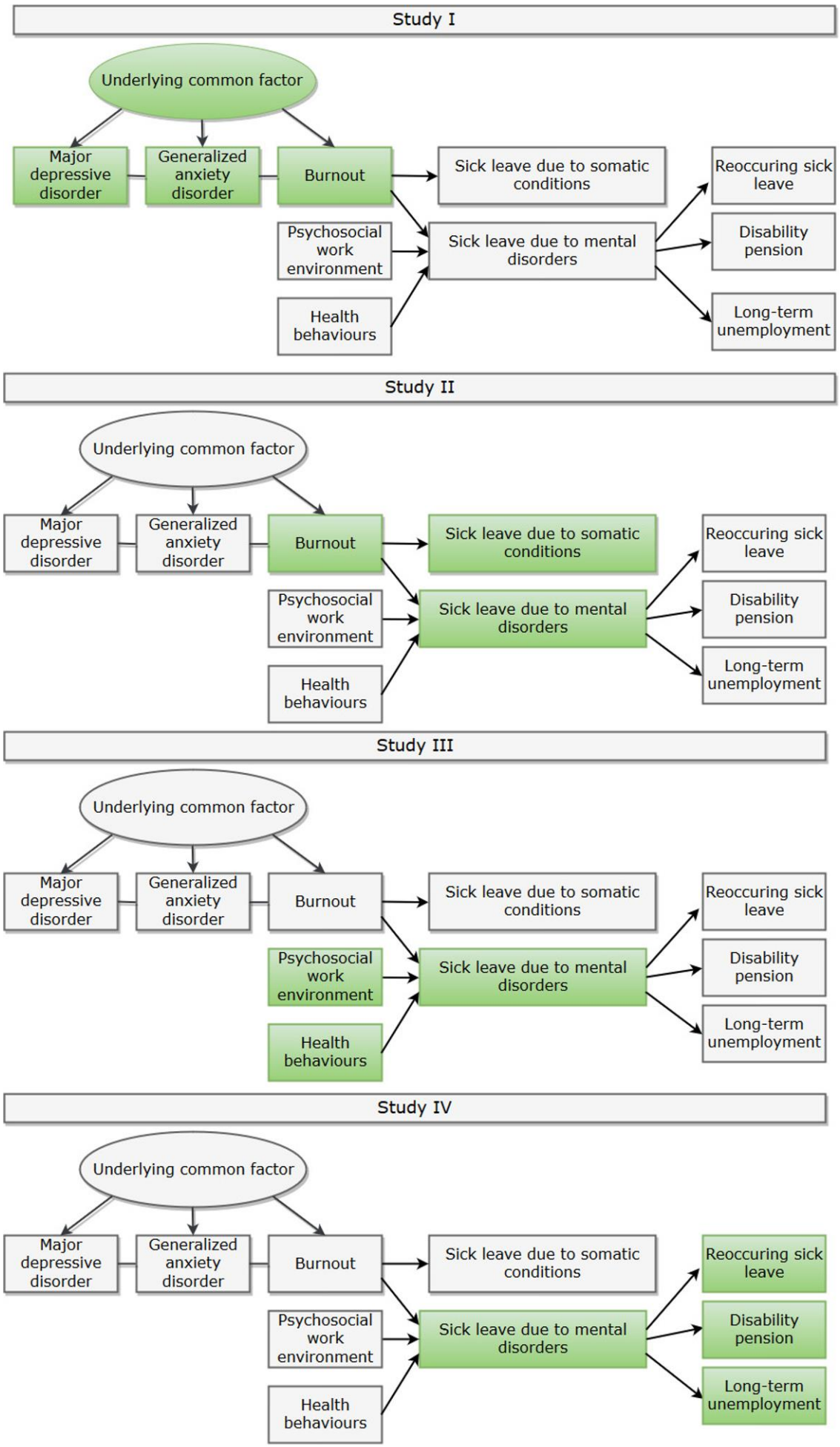

Figure 1: Overview of study I-IV

2 AIMS

2.1 OVERALL AIM

The overall aim of this thesis was to explore genetic and environmental aspects of burnout and sick leave due to stress-related and other mental disorders, including heritability, comorbidity, risk factors, and adverse outcomes.

2.2 SPECIFIC AIMS

Study I: To examine to what degree the covariation between major depressive disorder, generalized anxiety disorder and burnout was explained by common genetic and environmental factors, in women and men.

Study II: To assess whether the associations between burnout and sick leave due to stress-related mental disorders, other mental disorders, and somatic conditions was influenced by familial factors.

Study III: To investigate whether psychosocial work factors and health behaviors were risk factors for sick leave due to mental disorders and whether the associations were influenced by familial factors.

Study IV: To investigate the short and long-term effect of sick leave due to mental disorders on the outcomes reoccurring sick leave, disability pension and unemployment, while taking familial factors into account. An additional aim was to investigate if the effect differed between sick leave durations and diagnoses.

3 MATERIALS AND METHODS

3.1 DATA SOURCES

Studies included in this thesis were part of two larger projects "Factors of importance for burnout" and "the Swedish Twin project Of Disability pension and Sickness absence" (STODS) (116). Factors of importance for burnout contain cross-sectional data from the questionnaire study, the Study of Twin Adults Genes and Environment (STAGE). STODS contains all 119 907 twins from the population based Swedish Twin Registry (STR) born 1925-1990 and contains data from several large questionnaire studies, including STAGE, and population registry data that has been obtained and linked using the personal identification number of the twins. Data from the following sources was used in this thesis:

- STAGE was an extensive web-based questionnaire study, where an invitation to participate was sent to all twins in the STR born 1959-1985 (N= 42 582) in 2004-2006. STAGE had a response rate of 60%, hence the sample contains 25 496 individuals (25 378 in the data delivery used in study one) whereof 70% were complete twin pairs. A telephone interview was also offered as an alternative to the web-based response. STAGE included questions to assess zygosity, the Pines Burnout Measure, the Swedish Demand-Control-Support questionnaire as well as questions on alcohol use, smoking, and physical activity. STAGE also contained questions regarding sociodemographics and health status. More information about STAGE is available from (117, 118).
- The Social Insurance Agency's database MicroData for Analyses of the Social insurance (MiDAS) (119). MiDAS contains information about all sick-leave spells and disability pensions reimbursed by the Social Insurance Agency since 1994 including dates, grade (full time or part time), duration, and diagnosis. Sick-leave diagnoses are available from 2005 onwards.
- The longitudinal integration database for health, insurance and labor market studies register (LISA by Swedish acronym) held by Statistics Sweden, that contains information about demographics, education, and work sector (120).
- The cause of death register, held by the National Board of Health and Welfare, that contains death dates of Swedish residents (121).
- The National Patient Registry held by the National Board of Health and Welfare, which contains dates and diagnoses of hospital admissions was used for additional analyses included in the thesis (122).

3.2 STUDY DESIGN

Study I had a cross-sectional design that used only STAGE questionnaire data. Studies II, III, and IV had a prospective cohort design. Study II and III used STAGE to measure exposures, and used the MiDAS register for the outcomes, while study IV was completely register based.

3.3 INCLUSION/EXCLUSION CRITERIA AND STUDY POPULATION

Figure 2 contains a description on how the study populations were selected for the four studies, including exclusion and inclusion criteria.

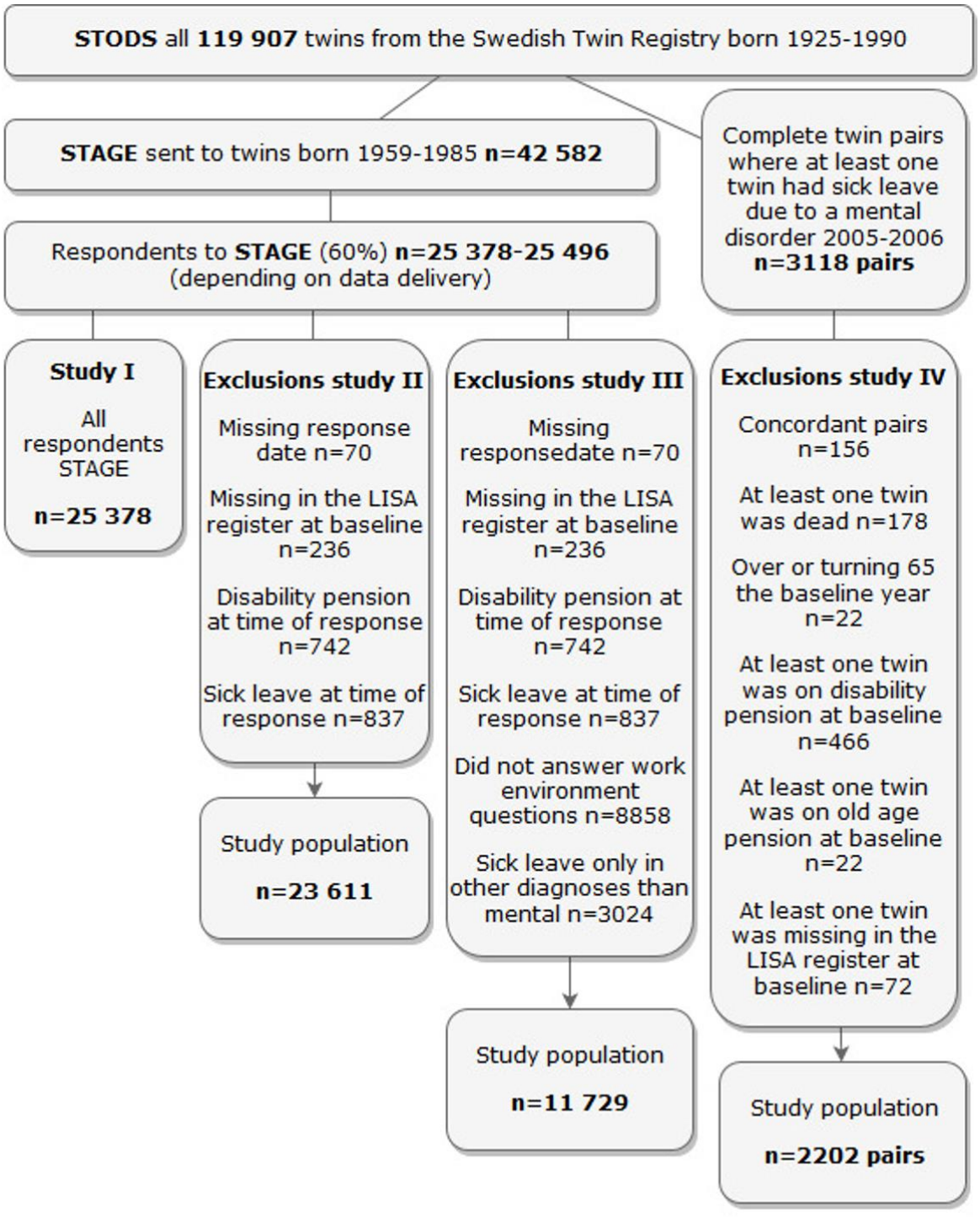

Figure 2: Inclusion and exclusion criteria and study population for study I-IV

3.4 VARIABLES

3.4.1 Burnout

Burnout was a central variable in studies I and II. Burnout was measured with the Pines Burnout Measure, included in the STAGE questionnaire. The short version with three questions was used, enquiring how often the participant had "felt down", "felt emotionally exhausted" and "felt ran down" the past 12 months, with responses 1=never, 2=once or a couple of times, 3=seldom, 4=sometimes, 5=often, 6=most of the time, and 7=all the time, was included and the mean value was calculated. Burnout was used as a continuous variable in regression analyses. However, due to the fact that multivariate biometric twin models were used with other binary variables, a categorical variable also had to be created. We used 4 groups: no burnout (1–2.99), risk of burnout (3–3.99), burnout (4–4.99), and severe burnout (5-7). The severe burnout group had no concordant dizygotic male twin pairs which made it impossible to use for sex limitation models. In study I the two highest categories were collapsed in order to further investigate sex differences. In study II the lack of concordant male dizygotic pairs was also a problem in the sick-leave variables, consequently we used men and women combined. The Pines Burnout Measure has been found to have good construct validity, it correlates highly (0.9) with the full version of the Pines Burnout Measure (38). Cronbach's alpha was 0.89 in study I and 0.87 in study II. Since the Pines Burnout Measure is not a clinical instrument, there is no clear cutoff in the Pines Burnout Measure where a person can be considered "burned out", however, Pines has stated that 4 is a critical level for burnout (25). We used cutoffs based on this as well as on previous studies (36, 37). As an additional analysis for this thesis, I also calculated the mean burnout levels of those that were on sick leave or disability pension when responding to STAGE, in order to further investigate these cutoffs.

3.4.2 Major Depressive Disorder

In study I, self-reported lifetime history of major depressive disorder was included. Thirty-eight questions in STAGE were used to measure this. An initial question was posed in the web-based questionnaire asking if the participant ever had felt depressed for two weeks in a row or more. If they answered yes they got asked the follow-up questions assessing the diagnostic criteria for major depressive disorder. Questions were based on the Structured Clinical Interview for DSM-IV Disorders (123) that uses criteria for major depressive disorder in the DSM-IV (57). Criteria A, C, and E had to be fulfilled in order for the participant to be classified as having had major depressive disorder (see Table 2). The validity of assessing the diagnostic criteria using a web-based questionnaire compared with structured clinical interviews have been studied with varied results (124-126). However, the genetic variance has been found to be captured well compared to a structured clinical interview (127, 128).

3.4.3 Generalized Anxiety Disorder

In study I self-reported lifetime history of generalized anxiety disorder was included. Twenty-three questions, with an initial question asking if the participant had felt anxious most of the time for more than one month, followed by questions assessing the diagnostic criteria if the person answered yes. The measure of generalized anxiety disorder was also based on Structured Clinical Interview for DSM-IV Disorders (123). Criteria A and C in DSM IV had to be present in order for the participant to be classified as having had generalized anxiety disorder (See Table 2) (57).

3.4.4 Sick leave

Sick leave was a major focus in study II, III, and IV. The MiDAS register was used to identify cases of sick leave i.e., sick leave that was reimbursed by the Social Insurance Agency. This means only spells that were longer than 14 days, however, in cases where the person on sick leave was unemployed, on parental leave, self-employed, or had a certain chronic disease or disability, shorter spells may also occur in the register. Both study II and III used cumulative incidence of sick leave in approximately 5-year follow-up time as the outcome measure. In study II, all sick-leave spells were included but stress-related mental diagnoses (ICD-10 F43), other mental diagnoses (rest of the F chapter), and somatic conditions (all other diagnoses) were analyzed separately. The outcome was measured in a hierarchal way i.e., if a sick-leave spell with a stress-related mental diagnosis was present the participant was placed in that group, even if sick-leave spells with other diagnoses were also present. If both a mental sick-leave spell and somatic sick-leave spell were present, the participant was categorized in the mental group. This approach was used as mental disorders, particularly stress-related mental disorders, were the main focus of this thesis. In study III, however, we did not have sufficient power to investigate stress-related mental diagnoses separately. Instead, sick-leave spells with a mental diagnosis was considered and the sick-leave variable was binary i.e., if there was any sick leave spell with the diagnostic code F00 to F99 during follow up or not. Those with sick leave spells in other diagnoses only were excluded in order to have a healthy reference category. In study IV the exposure measure was if there was a current or new sick-leave spell due to a mental disorder during the exposure window (2005-2006). Duration of the sick-leave spell was also considered in this study in terms of net days, where two half days are considered one net day. Type of mental diagnosis was also included, depressive disorder (ICD-10 code F32-33), anxiety disorder (ICD-10 code F40-42), stress-related disorder (ICD-10 code F43) and other mental disorders (remainder of the F chapter). Since we used a survival analysis the outcome measure was the first date of reoccurring sick leave, all diagnoses were included.

3.4.5 Psychosocial work environment

In study III, the Swedish translation of the job demand- control- support model by Karasek and Theorell was used (129). The measure has been found to have satisfactory validity and reliability (129). It includes questions of job demands such as “Does your job require you to work very fast?” control such as “Do you have the possibility to decide for yourself how to

carry out your work?" and support such as "There is good collegiality at work", for a list of all questions see (129). Answers were on a four-point Likert scale where: 1=agree completely, 2=agree somewhat, 3=do not really agree, and 4=do not agree at all. The mean scores were calculated and a categorical variable was created, using the medians of the variables as cutoff-points. Having high demands and high control was defined as an active job, low demands and low control as a passive job, low demands and high control as a low strain job, and high demands and low control as having job strain. A sub group to work strain with those that also has low social support was also used, called iso-strain (85, 86).

3.4.6 Health behaviors

Study III included measures of health behaviors from STAGE. Alcohol use was measured as grams per week from questions inquiring about type, amount, and frequency of alcohol consumption and the guidelines for "risk use" of alcohol (9 standard drinks per week for women and 14 for men) from the Swedish National Institute of Public Health were used to select cutoff points (130). Light-moderate consumers and abstainers were used as a reference category. Smoking used the categories current smokers and non-smokers, and the questions "Have you ever smoked or used snuff", "Do you currently smoke cigarettes?" and "Do you currently smoke cigarettes occasionally or at parties?" were used to define the groups (114). Physical activity was measured using the question "Rate your current physical activity level on a scale from 1 to 10; 1=very low (sedentary, mainly sitting), 5=moderate physical activity (a few walks a week), and 10=very high (sports/jogging several times a week)". Five categories were used: none (1 to 2), low (3 to 4), moderate (5 to 6), high (7 to 8), and vigorous (9 to 10) (131). We collapsed the categories "none" and "low" due to low numbers of respondents and vigorous was used as the reference category.

3.4.7 Long-term unemployment

In study IV, being long-term unemployed was defined as being unemployed for more than 180 days in a calendar year based on the LISA register data, as we only had access to number of days per year and not exact dates. The information in LISA has been collected from the Swedish National Employment Office and includes those registered as unemployed with the agency. The cutoff point 180 days has been used in previous studies (132, 133).

3.4.8 Disability pension

In study IV where disability pension was used as an outcome variable, the first day the individual started receiving disability pension was extracted from the MiDAS register. All diagnoses and both full and part time disability pension were included.

3.4.9 Zygosity

Zygosity refers to whether the twins are monozygotic or dizygotic and was used in all studies. The STR uses a questionnaire to measure zygosity that enquires about physical similarity in childhood, including questions such as "Were you and your twin partner while growing up "like two peas in a pod" or you were "no more similar than siblings in general" terms of

appearance?". This measure is included in all the questionnaire studies performed by the STR (134). However, zygosity measured based on DNA is becoming more prevalent and is now available for 13% of the same sex twins in the STR. In two small subsamples of the registry, the questionnaire has been validated against DNA testing and was found to be 98% accurate (134, 135), similar to findings from other countries, such as in the Danish (136) and Norwegian twin registries (137).

3.4.10 Other covariates

Sex and age was included in all studies. In study III education (highest level of completed education registered in the LISA database), previous sick leave (presence of sick leave 2 years prior to the response date to STAGE in MiDAS), and self-rated health (how do you rate your general health; 1-5) was also adjusted for in the analysis of the whole sample. Study IV used the censoring variables date of death from the cause of death registry, and old age pension from the LISA register, and emigration, which was identified in the LISA register. If an individual was missing from the register for 2 years in a row they were considered as having emigrated.

3.4.11 Inpatient care

Having had inpatient care for any diagnosis within two years prior to the exposure sick-leave spell was identified in the National Patient Registry. The variable was only used in the additional analysis for study IV, see paragraph 3.3.5.1.

3.5 STATISTICAL ANALYSES

In this thesis two different types of methods were used, biometric twin models (Study I-II) and regression analysis with co-twin control (Study II-IV). Biometric twins models were performed using OpenMx software (138) run within the R environment (139). Regression analyses with co-twin control were performed in STATA IC 12. In all studies 95% confidence intervals (CI) were used and p-values less than 0.05 were considered statistically significant. Questionnaire responses/answers "don´t know/don't want to answer", were considered as missing values.

3.5.1 Biometric twin models

In biometric twin models, it is assumed the total phenotypic variance P is the sum of the additive genetic influences A, the non-additive genetic influences D, the shared environmental influences C and the unique environmental influences E (140).

P=A+D+C+E.

A refers to the sum of the effects of the alleles that influence the trait. Hence this parameter is set to correlate 1 between monozygotic twin pairs and 0.5 between dizygotic twin pairs. D refers to other genetic influences that involve interaction between alleles in the same gene or different genes. Hence this parameter is set to correlate 1 between monozygotic twin pairs

and 0.25 between dizygotic twin pairs. C represents the environment that is shared between the twins and hence is set to be 1 for both twin types. E represents the environment that is unique to each twin and the correlation is set to be 0 for both twin types, this parameter also contains measurement error (140). D and C cannot be estimated in the same models in samples containing only twins reared together (140). Figure 3 shows a path diagram of an ACE and ADE univariate model.

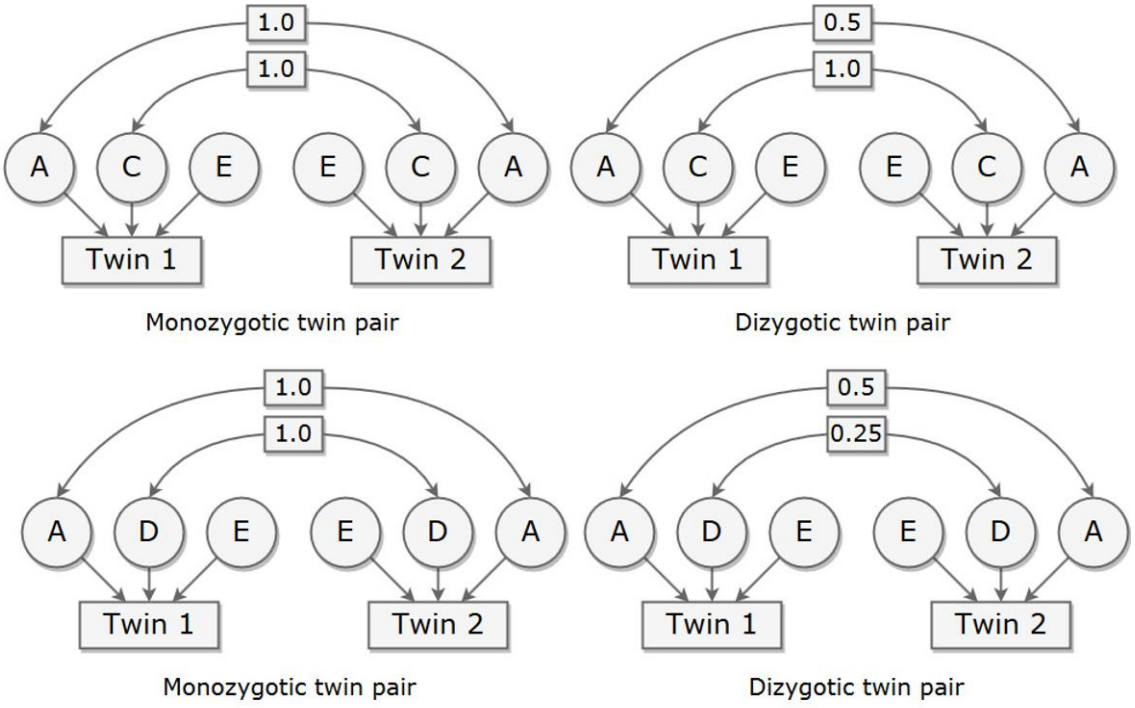

Figure 3: ACE and ADE univariate biometric twin models

Including opposite sex twins makes it possible to assess qualitative sex differences (whether same genes are underpinning the phenotype in men and women) by examining if the genetic correlation can be set to 0.5 in opposite sex dizygotic twins. Liability threshold models were used for categorical variables, where it is assumed that there is an underlying liability to the categorical variables that is normally distributed. Both discordant and concordant pairs as well as single twins were included in these analyses, as this provides the most information. Models are based on the variance (univariate models) or covariance matrixes (multivariate models) among monozygotic and dizygotic twins.

First, saturated models were built and compared with a nested model that restricts the thresholds to be equal between twin 1 and twin 2 in a pair (randomly assigned) and between monozygotic and dizygotic twins, as this is an assumption of the models. In this type of analyses a more parsimonious model is preferred, hence, full models were compared to more parsimonious sub-models, and if the fit was not significantly different, the more parsimonious model was chosen (141). Where models were nested likelihood ratio chi-square statistic were used for this purpose, in case of non-nested models Bayesian Information Criterion (BIC) values were used to determine the best fitting most parsimonious model, where a lower value indicate the better fit (142, 143).

There are different types of multivariate models. In a Cholesky model, one of each of the factors per phenotype (A, C/D, E) is included. In a common factor common pathway model, factors load onto a latent common factor with a path to each phenotype, as well as an A, C/D, and E factor with an independent path to each phenotype. In a common factor independent pathway model, there is one shared A, C/D, and E factor with a path to each phenotype and a separate A , C/D, and E factor per phenotype (Figure 4).

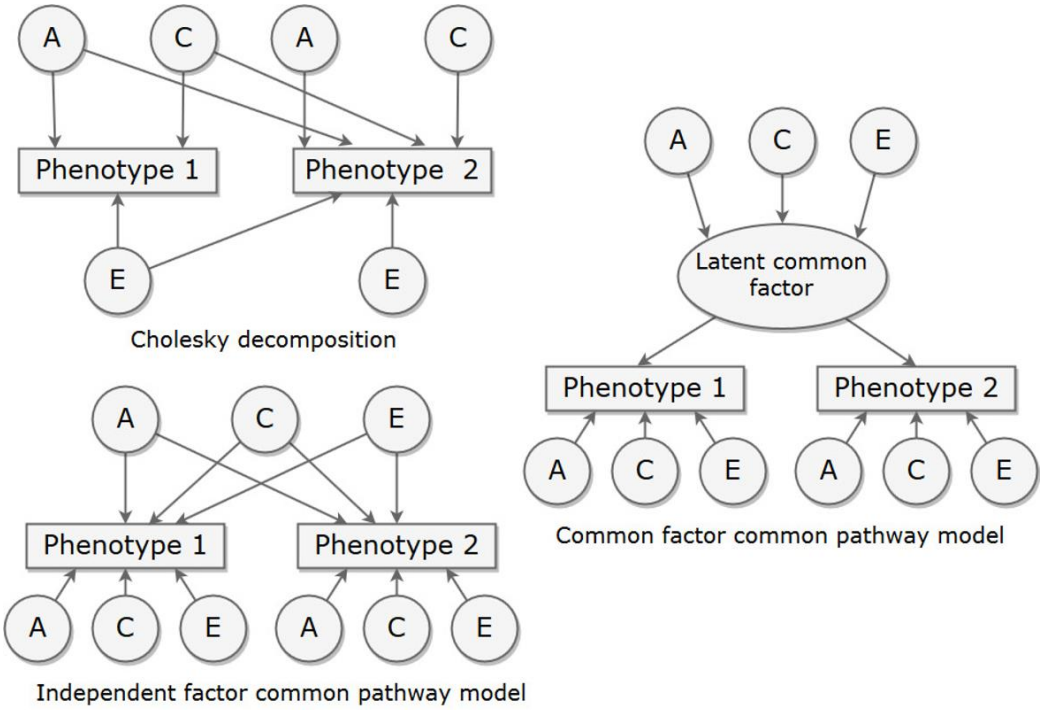

Figure 4: Three different multivariate ACE biometric twin models

3.5.1 Regression analyses with co-twin control

Regression analyses are commonly used in epidemiology when studying how measured risk factors explain the variation in an outcome, since they are flexible and allow adjustments for confounding effects by other variables in addition to interaction effects (144). In this thesis, logistic regression calculating odds ratios (OR) and cox proportional hazards regression models calculation hazard ratios (HR) were used. In cox regression models time-to event is analyzed and the models investigate how survival varies depending on the exposure variables. In logistic regression, person time is not used and models are investigating the probability of a binary outcome given a set of covariates. Logistic regression was used in study one and two, even though we had access to specific dates, since we were interested in sick leave due to mental disorders during the follow-up time, rather than time to event. When using a twin cohort for regression analyses, it must be taken into account in the analysis that the twins in a pair are not statistically independent (144). We used the clustered robust standard error for this purpose.

Discordant twins were used in matched analysis (co-twin control), similar to a case-control study where the factors that the twins are matched on (familial factors) are adjusted for (145). Hence, this conditional regression analysis, adjusts for a large number of unmeasured,

potential confounders (144). Doing both an analysis of the whole sample and a matched analysis is recommended as this gives the most information (144). Comparing the analysis of the whole sample to the conditional analysis of the discordant twin pairs can then be used to investigate the impact of familial factors on the associations (146). If the OR or HR is increased in the analysis of the whole sample, it seems that the exposure is a risk factor for the outcome. If the estimates are reduced in the conditional analysis, it indicates that this association is explained by familial factors. The analysis can also be stratified on zygosity, and if the OR or HR is higher in dizygotic twins compared to monozygotic twins it would indicate that the association is explained by genetic factors, as the monozygotic twins are more closely matched on genetics (146).

3.5.2 Study I

In this study, univariate and different types of multivariate biometric twin models were performed. The univariate models tested for qualitative and quantitative sex differences, using five zygosity groups, monozygotic females, monozygotic males, dizygotic females, dizygotic males, and opposite sex dizygotic pairs. Full ACE and ADE models allowing for qualitative and quantitative sex differences were built and tested against more parsimonious sub-models restricting the sex differences and removing parameters. Three different multivariate models were compared; the Cholesky decomposition, the common factor independent pathway model, and the common factor common pathway model, with one latent factor, using two zygosity groups, monozygotic and dizygotic pairs, including opposite sex twins and with men and women combined. More parsimonious sub-models were then tested against the best fitting model.

3.5.3 Study II

In this study logistic regression analyses were used, of the whole sample and co-twin control, as well as a bivariate Cholesky twin model. The logistic regression analysis of the whole sample (n=23 611) was adjusted for sex and age. The co-twin analysis included complete same-sex twin pairs discordant for the outcomes (sick leave due to stress-related mental disorders: 141 pairs, other mental disorders: 135 pairs, and somatic conditions: 1071 pairs) and was also stratified on zygosity. In the Cholesky models the entire sample was included (n=23 611). A two-group model where women and men were combined, including the opposite-sex twins, was used. Full ACE and ADE models were built and tested against more parsimonious sub-models. The proportion of the phenotypic correlations that were explained by genetic effects was calculated from the final model and additional analyses were performed with sex as a covariate.

3.5.3.1 Additional analyses

Individuals that were on sick leave or disability pension when responding to STAGE were identified as such in the MiDAS register and the mean score of Pines Burnout Measure was calculated. Moreover, individuals were stratified on sick-leave/disability pension diagnosis: sick leave/disability pension due to stress-related mental disorders (ICD-10 code F43), sick

leave/disability pension due to mental disorders (whole F chapter including F43) and somatic conditions (all others except for the F chapter, including missing diagnoses).

3.5.4 Study III

The main analysis in this study was logistic regression to assess ORs. In the analyses of the whole sample (n=11 729), we adjusted for the covariates sex, age, education, self-rated heath, and previous sick leave in steps. Quadratic terms were tested for the continuous predictors, and interaction terms between the work environment and health behaviors were tested in the models. Co-twin analyses were also performed for the discordant complete same sex twin pairs (n=161 pairs), but not stratified on zygosity due to power constraints.

3.5.5 Study IV

In this study we used cox proportional hazards regression models with co-twin control to calculate HRs. Only discordant pairs were included hence the analyses of the whole sample and the co-twin control models contained the same amount of observations (2202 twin pairs). The analyses of the whole sample were adjusted for sex and age separately and the co-twin model contained both same and opposite sexed twins, as stratified analyses showed no major sex differences or differences between same sex and opposite sex DZ twins. Follow up was censored for old age pension, death, emigration, disability pension, the respective outcomes and end of the study (December 31, 2012). Time varying covariates (tvc) were used to split follow up time in case of non-proportional hazards, assessed with the proportional hazards post-estimation test.

3.5.5.1 Additional analysis

Inpatient care and long-term unemployment in the two years prior to starting the exposure sick-leave spell was identified in the patient and LISA registers for the cases and the co-twins. Prevalence of inpatient care and unemployment were calculated for each group and differences between cases and co-twins were tested with chi-square test.

3.6 ETHICAL ASPECTS

Studies included in this thesis has been a part of two larger projects that have been approved by the regional ethics committee board in Stockholm (Risk factors for and consequences of being sickness absent/disability pensioned Dnr: 2007/524-31, Dnr: 2010/1346-32/5 and Dnr: 2014/311-32 and a twin study of factors associated with burnout Dnr: 2009/2053-31/5 and 2014/1043-32). Ethical permissions were obtained for all extractions from the population registries and all personal identification numbers or other ways to identify people in these extractions have been censored. Thus, data can only be used to draw conclusions on population level and information on individuals cannot be disclosed.

4 RESULTS

An overview of the main results can be found in Table 3.

Table 3: Overview of the aims, methods and main results				
Study	**I**	**II**	**III**	**IV**
Aim	To examine to what degree the covariation between major depressive disorder, generalized anxiety disorder and burnout was explained by common genetic and environmental factors, in women and men.	To assess whether the associations between burnout and sick leave due to stress-related mental disorders, other mental disorders, and somatic conditions were influenced by familial factors.	To investigate whether psychosocial work factors and health behaviors were risk factors for sick leave due to mental disorders and whether the associations were influenced by familial factors.	To investigate the short and long-term effect of sick leave due to mental disorders on the outcomes reoccurring sick leave, disability pension and unemployment, while taking familial factors into account.
Data sources	STAGE	STAGE, MiDAS, LISA	STAGE, MiDAS, LISA	STODS, MiDAS, LISA, Cause of death register
Study population	N=25 378	N=23 611	N=11 729	N= 4404 (2202 Pairs)
Design	Cross-sectional	Prospective cohort	Prospective cohort	Prospective cohort
Exposure	Major depressive disorder, generalized anxiety disorder, burnout	Burnout	Psychosocial work environment, risk use of alcohol, smoking and low physical activity	Sick leave due to mental disorders
Outcome		Sick leave due to stress-related mental disorders, other mental disorders and somatic conditions	Sick leave due to mental disorders	Reoccurring sick leave, disability pension, unemployment
Main analysis	Multivariate biometric twin model	Logistic regression with co-twin control and multivariate biometric twin model	Logistic regression with co-twin control	Cox regression with co-twin control
Factors included in analyses	Sex and zygosity	Sex, age and zygosity	Sex, age, education, self-rated heath and previous sick leave	Sex, age and zygosity
Main Finding	The covariation between Major depressive disorder, generalized anxiety disorder and burnout was explained by an underlying factor influenced by genetics (58%) and unique environment (42%).	The covariation between burnout and sick leave due to stress-related and other mental disorders was explained by genetic factors. Burnout was a risk factor for sick leave due to somatic conditions independent of familial factors.	High job demands, job strain and iso-strain were risk factors for sick leave due to mental disorders independent of familial factors. The health behaviors were not independently associated with sick leave due to mental disorders.	Sick leave due to mental disorders increased the risk for reoccurring sick leave for two years, disability pension and unemployment independent of familial factors.

Overall, the results show that burnout share a predisposition with major depressive disorder and generalized anxiety disorder, that is largely genetic. Genetic factors were also of importance in the transition from burnout to sick leave due to mental disorders and the correlations were similar between burnout and stress-related mental disorders and other mental disorders. Job strain was a risk factor for sick leave due to mental disorders independent of familial factors and sick leave due to mental disorders increased the risk for reoccurring sick leave for two years, disability pension and long-term unemployment independent of familial factors.

4.1 MAIN RESULTS STUDY I

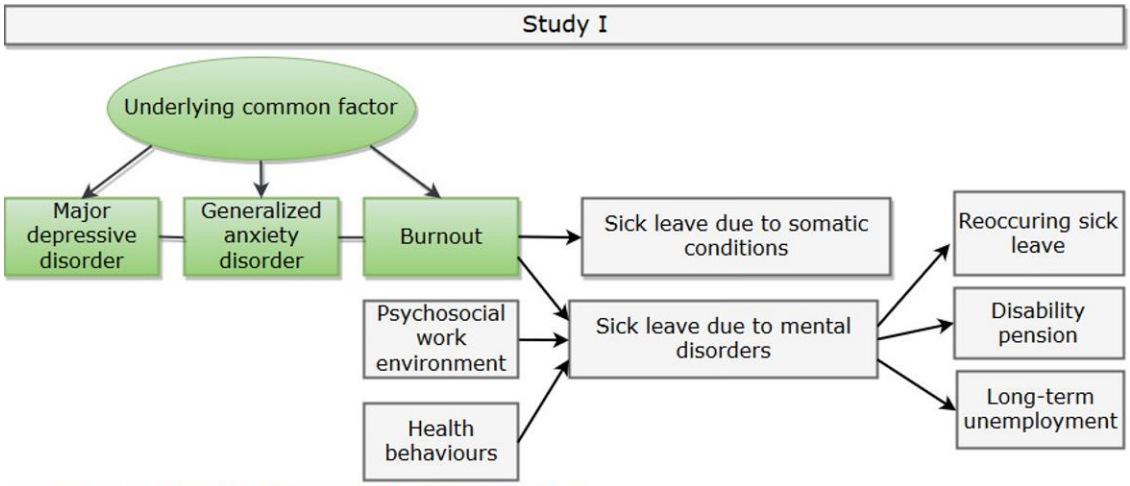

Figure 5: Study I in relation to the other studies

In study I (Figure 5) of 25 378 twins the prevalence was 11% (n=2821) for major depressive disorder, 4% (n=935) for generalized anxiety disorder and 17% (n=4306) for burnout. In univariate biometric twin models, we found no statistically significant sex differences and AE models gave the best fit for major depressive disorder, generalized anxiety disorder, and burnout. The heritability was 45% for major depressive disorder, 49% for generalized anxiety disorder, and 38% for burnout.

Phenotypic correlations were 0.71 between major depressive disorder and generalized anxiety disorder, 0.58 between major depressive disorder and burnout, and 0.53 between generalized anxiety disorder and burnout. In the multivariate analysis a common pathway AE model without a phenotypic specific a path to major depressive disorder was found to be the best fit. Figure 6 contains the path estimates for the best fitting model, the covariance components can be obtained by squaring the estimates. Results indicate that there was a latent common factor that explains the covariation and that this common factor is influenced to 58% by genetics and to 42% by unique environment. This common factor explained the majority of the variation of major depressive disorder (77%) and generalized anxiety disorder (69%), but less of the variation in burnout (44%). Phenotype specific genetic factors explained 11% of the variation in both generalized anxiety disorder and burnout and the remainder of the variation (45% for burnout, 23% for major depressive disorder and 20% for generalized anxiety disorder) was explained by phenotypic specific unique environment.

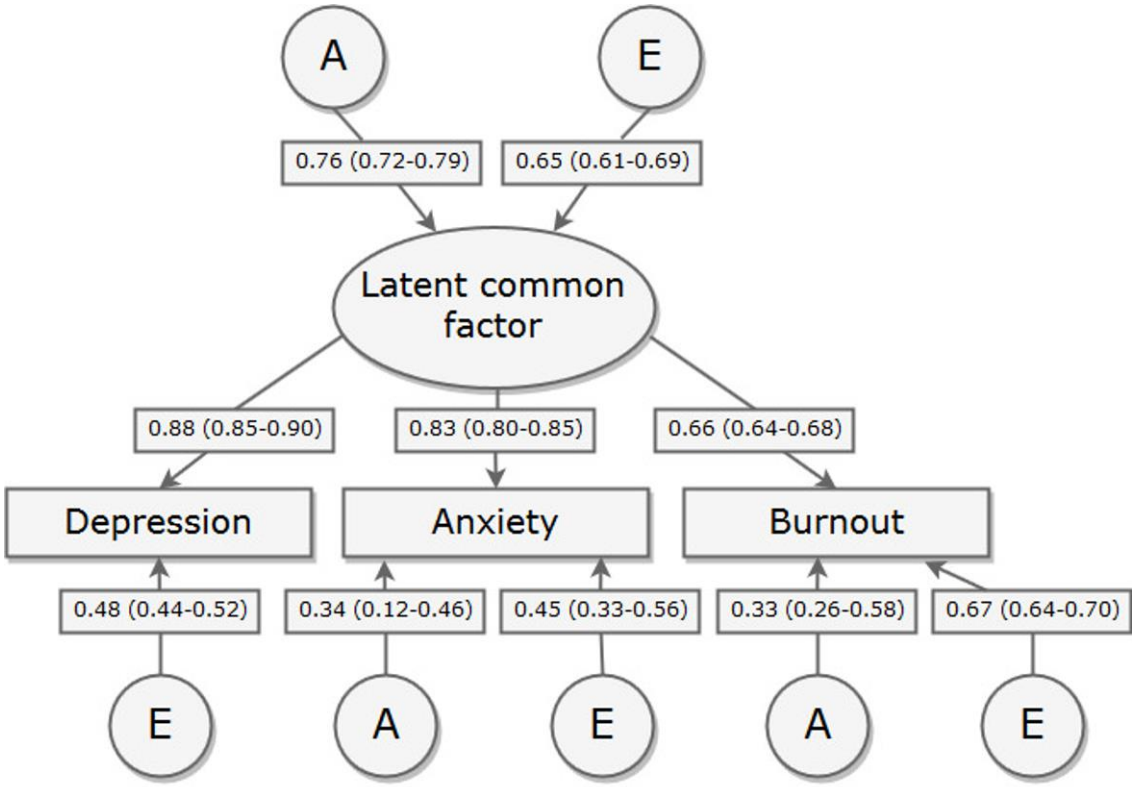

Figure 6: Path estimates with 95%confidence intervals from the best fitting common factor common pathway model for the covariation between depression, anxiety and burnout.

4.2 MAIN RESULTS STUDY II

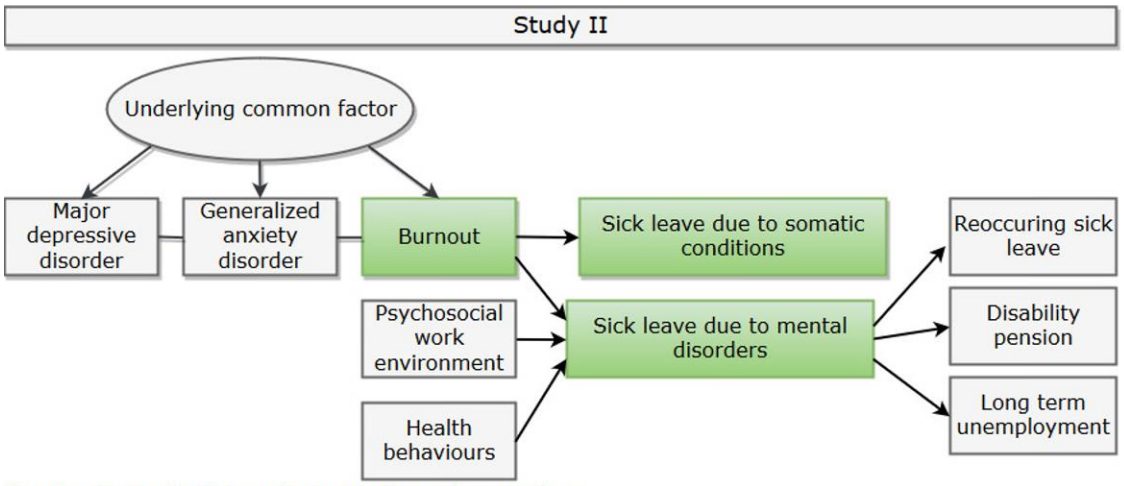

Figure 7: Study II in relation to the other studies

In study II (Figure 7), among the 23 611 twins, we found that 26% of the sample (n=6158) had sick leave during follow up, 3.1% (n=736) due to a stress-related mental disorder and 3.1% (n=743) due to another mental disorder.

In the logistic regression analyses, burnout was a strong risk factor for sick leave due to stress-related (OR: 1.47, CI: 1.39–1.56) and other mental disorders (OR: 1.63, CI: 1.54–1.73) and a significant but less strong risk factor for sick leave due to somatic conditions (OR: 1.10, CI:1.07–1.13). The associations were not largely influenced by adjusting for sex and age. However, the co-twin analyses showed that the associations between burnout and sick leave due to stress-related (OR: 1.02, CI: 0.83–1.25) as well as other mental disorders (OR: 1.19, CI: 0.99–1.43) seems to be explained by familial factors, while the association between burnout and sick leave due to somatic conditions did not seem influenced by these factors (OR: 1.10, CI: 1.02–1.19).

In the biometric twin model an AE model without a unique environmental correlation between the phenotypes was the best fit for both the models (Figure 8). The heritability was 37% for burnout, 58% for sick leave due to stress-related mental disorders and 54% for sick leave due to other mental disorders. The phenotypic correlation between burnout and sick leave due to stress-related mental disorders was 0.26 and the phenotypic correlation between burnout and sick leave due to other mental disorders was 0.30. Both phenotypic correlations were explained by genetic factors.

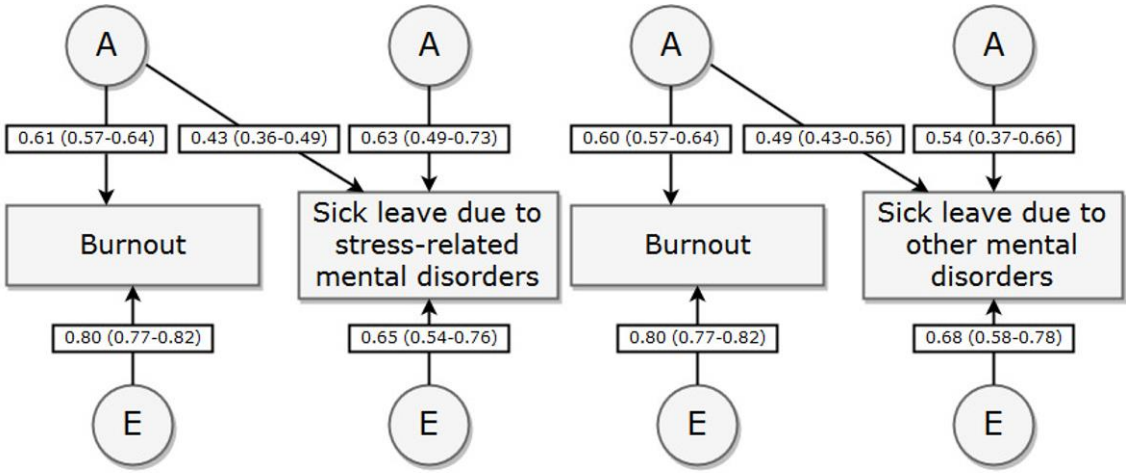

Figure 8: Path estimates with 95%confidence intervals from the best fitting Cholesky models for burnout and sick leave due to stress-related mental disorders (left) and burnout and other mental disorders (right).

4.2.1 Additional analyses: Burnout among those on sick leave/disability pension

The burnout scores of those individuals on sick leave or disability pension at the time of responding to STAGE stratified on diagnoses can be seen in Table 4. The mean burnout score was above four for those on sick leave due to mental disorders and above three for those on sick leave due to somatic conditions.

Table 4: Burnout among those on sick leave or disability pension at the time of answering STAGE

Pines Burnout Measure	**All** n=1649	**Sick leave/Disability pension due to somatic conditions** n=1024	**Sick leave/Disability pension due to mental disorders** n=625	**Sick leave/Disability pension due to stress-related mental disorders** n=130
Mean score (1-7)	3.6 (SD 1.7)	3.1(SD 1.6)	4.4 (SD 1.5)	4.8 (SD 1.1)
No burnout	505 (30.6%)	414 (40.4%)	91 (14.6%)	8 (6.2%)
Risk for burnout	208 (12.6%)	151 (14.7%)	57 (9.1%)	9 (6.9%)
Burnout	299 (18.1%)	170 (16.6%)	129 (20.6%)	32 (24.6%)
Severe burnout	426 (25.8%)	152 (14.8%)	274 (43.8%)	66 (50.8%)
Missing	211 (12.8%)	137 (13.4%)	74 (11.8%)	15 (11.5%)

Note: Stress-related mental disorders (ICD 10 code F43) are a sub group of mental disorders (whole F chapter).

4.3 MAIN RESULTS STUDY III

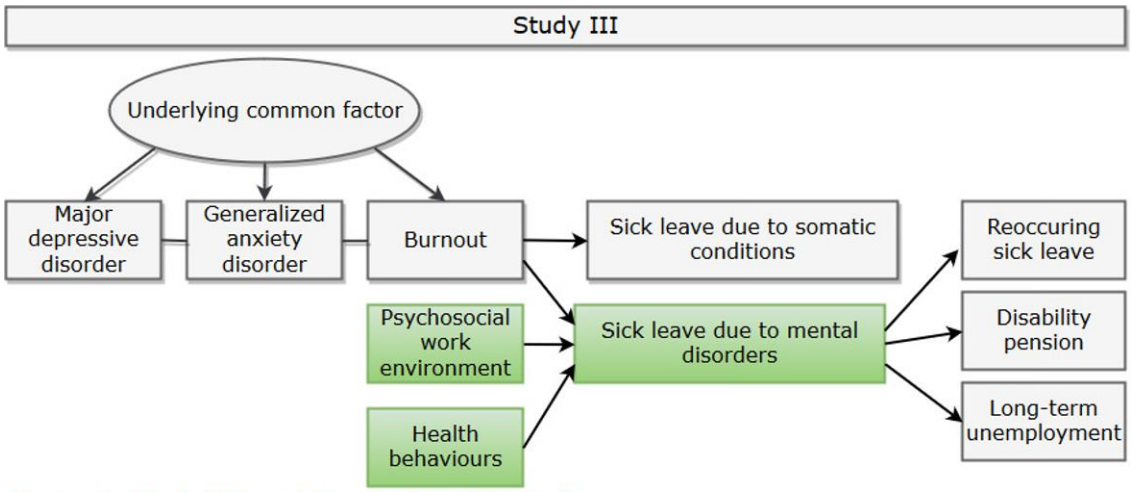

Figure 9: Study III in relation to the other studies

In study III (Figure 9) we found that eight percent (n=972) of the sample of 11 729 twins, had sick leave due to a mental disorder during the approximately five-year follow up and almost three quarters (n=717) were women.

Job strain and iso-strain were risk factors for sick leave due to mental disorders, after controlling for included confounders (job strain OR: 1.38, CI: 1.06–1.79, iso-strain OR: 1.37, CI: 1.03–1.82) and familial factors (job strain OR: 4.42, CI: 1.98–9.86, iso-strain OR: 5.03, CI: 2.04–12.44) . When analyzing job demands, control and support separately, job demands was a significant risk factor, even after controlling for confounders (OR: 1.47, CI: 1.26–1.71) and familial factors (OR: 1.91,CI: 1.18–3.11), while the association between control and support and sick leave due to mental disorders, was present in the crude analyses (control OR: 1.25, CI: 1.12–1.40, support OR: 1.26, CI: 1.08–1.47), but disappeared in adjusted analyses (control OR: 0.98, CI: 0.84–1.15, support OR: 1.05, CI: 0.86–1.28).

None of the health behaviors showed independent associations with the outcome. Alcohol use was not associated with the outcome even in crude analysis (OR: 1.15, CI: 0.93–1.41). Smoking was associated in adjusted analysis of the whole sample (OR: 1.29, CI: 1.09–1.54), however, this seems to be explained by familial factors as the association was not present in the co-twin analysis (OR: 0.50, CI: 0.23–1.07). Physical activity showed an association in the crude (none/low OR: 1.42, CI: 1.13–1.77, moderate OR: 1.26, CI: 1.02–1.56), but not adjusted analysis (none low OR: 0.91, CI: 0.71–1.17, moderate OR: 0.81, CI: 0.64–1.02). Moreover, in the adjusted analysis high physical activity was found to be protective compared to vigorous (OR: 0.75, CI: 0.60–0.94).

Adjusting for the health behaviors did not impact on the associations between the work environment variables and sick leave due to mental disorders. No interactions between work environment and health behaviors were found.

4.4 MAIN RESULTS STUDY IV

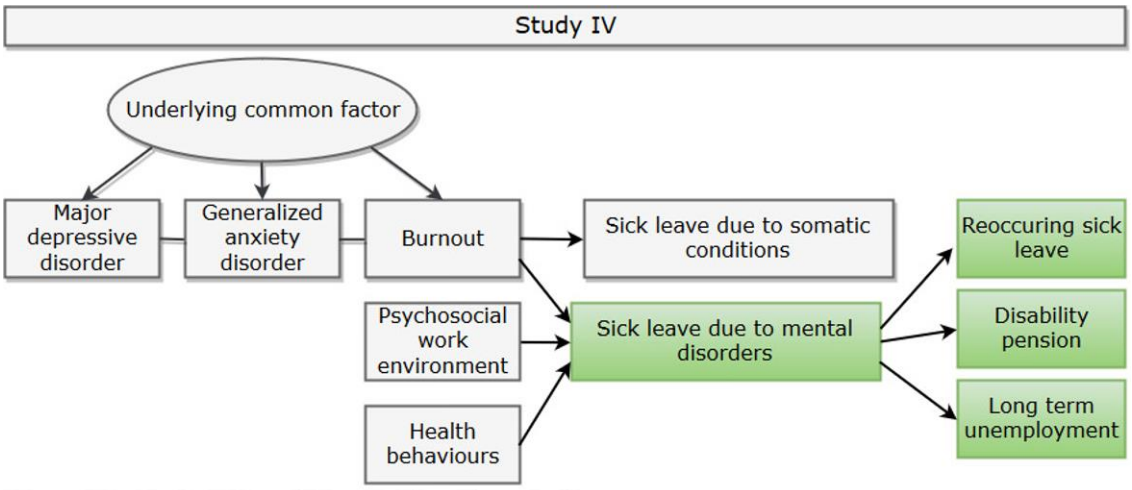

Figure 10: Study IV in relation to the other studies

In study IV (Figure 10), out of the 4404 twins, we found 50% (n=2221) had sick leave, 11% (n=464) disability pension, and 11 % (N=498) long term unemployment during the follow up.

The risk of reoccurring sick leave was more than three times higher for those with sick leave due to mental disorders compared with their co-twin for two years after the end of the initial sick-leave spell (HR: 3.64, CI: 3.24-4.08). After two years however, the risk was attenuated (HR: 1.42, CI: 1.24-1.62) and seems to be influences by genetic factors as no association was found in the analysis of monozygotic twins (HR: 0.83, CI: 0.65-1.06). There were no major differences for different durations or diagnoses of sick leave.

The risk of disability pension was more than 12 times higher for those with sick leave due to mental disorders, compared with their co-twin for a year after the end of the initial sick-leave spell (HR: 12.24, CI: 8.11-18.46). Subsequently those with sick leave due to mental disorders still had more than double the risk and this remained throughout the rest of the follow-up time (HR: 2.75, CI: 2.07-3.65). The risk of disability pension increased with longer duration of the sick-leave spells. Those with stress-related disorders had lower risk than those with other mental disorders in the unconditional analyses; however, this pattern was less clear in the conditional analyses.

Co-twin analysis showed that sick leave due to mental disorders doubled the risk for long-term unemployment consistently over the follow up time (HR: 1.99, CI: 1.72-2.31). The increased risk was seen in all durations of sick leave but was higher in those that had a sick-leave spell longer than 365 net days. The risk was higher for those with a diagnosis of depression, anxiety, or other mental disorders than for those with stress-related mental diagnosis.

4.4.1 Additional analyses: inpatient care and unemployment before the sick-leave spell

Seven percent (n=152) of those that had sick leave due to a mental disorder had inpatient care within two years of starting the exposure sick-leave spell, the corresponding number among their twin siblings without such sick leave was 5% (n=109). The difference was statistically significant ($p<0.01$). The number of inpatient care visits within two years of the exposure spell among the cases and co-twins can be found in Table 5. Among those with sick leave due to a mental disorder, 7% (n=148) had been unemployed for 180 days/year or more within two years before starting the exposure sick-leave spell, the corresponding number among their twin siblings without such sick leave was 6% (n=136). The difference was not statistically significant ($p= 0.46$).

Table 5: Number of inpatient care visits within 2 years before the exposure spell

Number of inpatient care visits	Cases	Co-Twins
0	2050 (93%)	2093 (95%)
1	121 (6%)	87 (4%)
2	22 (1%)	15 (1%)
3	≤ 8 (0%)	≤ 8 (0%)
4	≤ 8 (0%)	≤ 8 (0%)
7	≤ 8 (0%)	≤ 8 (0%)

5 DISCUSSION

5.1 MAIN FINDINGS

Burnout, major depressive disorder, and generalized anxiety disorder were highly correlated and the best fitting model indicated this was due to an underlying latent common factor mainly influenced by genetic factors, but also by unique environment. Burnout was to a large degree influenced by unique environmental factors not shared with major depressive disorder and generalized anxiety disorder. Burnout predicted sick leave due to mental disorders, and this association was explained by a shared genetic liability. However, burnout increased the risk of sick leave due to somatic conditions, independent of familial factors. High job demands, job strain and iso-strain were risk factors for sick leave due to mental disorders, independent of familial factors. Sick leave due to mental disorders increased the risk of reoccurring sick leave within two years, disability pension, and long-term unemployment independent of familial factors.

5.2 IMPLICATIONS

We found symptoms of burnout were very common, with 17% of the respondents to STAGE scoring above 4.0 on the Pines Burnout Measure, and that burnout was closely related to depression and anxiety. At the time of answering STAGE, 625 (2.4%) individuals were on sick leave or disability pension due to a mental disorder, and they had an average score of 4.4 on the Pines Burnout Measure. This high prevalence of burnout in this relatively young sample in 2005, is a cause for concern, since 35% of those with burnout went on to have sick leave in the 5 year follow up, 13% in a mental diagnosis and 22% in another diagnosis. And indeed, the levels of sick leave due to mental disorders, especially stress-related mental disorders, have increased in Sweden (2).

Our findings indicate that genetic predisposition was of importance in the transition from burnout to sick leave due to mental disorders, hence, genetic predisposition may help explain why some with burnout require sick leave and some do not. However, heritability is a measure of how much of the variation in a population is explained by genetics, and that depends on the amount of environmental variation in that population. Therefore, the fact that burnout and sick leave due to mental disorders are heritable does not mean societal changes cannot affect the prevalence. We found that poor psychosocial work environment on the other hand, seems to increase the risk of sick leave due to mental disorders regardless of familial predisposition. Those that had sick leave due to mental disorders had an increased risk of subsequent sick leave for two years, disability pension and long-term unemployment regardless of familial predisposition. Taken together these results confirm that burnout and sick leave due to mental disorders are issues of major public health concern that may have serious consequences, both for individuals and to society as a whole.

5.3 HERITABILITY OF BURNOUT, MENTAL DISORDERS, AND SICK LEAVE

The results indicate that there are genetic risk factors for burnout, depression, and anxiety as well as sick leave due to mental disorders, and that they are shared to a large extent. Twin studies on burnout are scarce and two twin studies from the Netherlands on the heritability of burnout had somewhat conflicting results. The previous results of the univariate analyses found burnout clustered in families due to shared environment (147), while the multivariate analyses of burnout and anxious depression found that the phenotypic correlation was 0.40 and genetic factors explained 66% of this correlation (107). This was lower than the phenotypic correlations we found in study I, perhaps due to that the Maslach Burnout Inventory was used in those previous studies that may be less correlated with depression than the Pines Burnout Measure used in this thesis.

The fact that depression and anxiety share genetic risk factors is in line with findings from several twin studies that found genetic correlations between 0.74–1.00 (148, 149). Moreover, sick leave (all diagnoses) (7, 110) and disability pension due to mental disorders (108, 109) have been found to be heritable in previous twin studies. However, a Norwegian twin study found that the association between depression and anxiety and sick leave due to mental disorders was influenced by both genetic and unique environmental factors (112). This differs from our finding on burnout and sick leave due to mental disorders, which we found to have completely separate unique environmental factors.

Our results of a shared genetic liability to burnout, depression, anxiety and sick leave due to mental disorders are also in line with results from non-twin studies. A longitudinal study from Finland found that burnout and depression have a reciprocal relationship i.e., burnout predicts depression and depression predicts burnout, in line with a shared genetic vulnerability (150). A shared genetic vulnerability for burnout and depression was also indicated in a previous study that found an increased risk for burnout, if a close family member had previously had depression (151). Molecular studies have also found that depression and anxiety share genetic risk factors (152). Moreover, a Finnish genome wide association study found no individual common genetic variants with a strong effect on job-related exhaustion, but did find an allelic variant that might be a weak risk factor for job-related exhaustion, and mark a candidate region for further studies of job-related and general exhaustion (153).

5.4 COMORBIDITY

We also found that burnout was a risk factor for sick leave in somatic conditions, independent of familial factors, even though the estimates were somewhat low. Somatic symptoms in those with exhaustion disorder is common (51), and are also included in the diagnostic criteria (Table 1). Burnout has been found to affect physical health (27-29), however, there are only a few studies (47). Prolonged psychosocial stress has a degenerative effect on the body in terms of sleep, muscle pain and fatigue (9). A poor psychosocial work environment has been found to be a risk factor for back pain (154). Burnout having an effect on pain may be the explanation for its association with sick leave due to somatic conditions since

musculoskeletal diagnoses including back pain, are very common as reasons for sick leave in Sweden (155). Burnout has also been studied in relation to immune function and inflammation with somewhat conflicting results (47). In a previous study of this sample, we found that physical illness as reported in STAGE was associated with burnout (156), so it is also possible that the exhaustion is caused by physical illness and is therefore associated with sick leave.

Alcohol risk use, smoking, and lack of physical activity did not predict sick leave due to mental disorders in this sample, and did not influence the association between psychosocial work environment and sick leave due to mental disorders. Consequently, even though there is an association between mental ill health and adverse health behaviors, there does not seem to be a direct effect of alcohol risk use, smoking and low physical activity on sick leave due to mental disorders in a population healthy enough to work. An excess mortality has been found among psychiatric patients (98, 99), however, a study found that alcohol use and smoking did not affect the association between sick leave due to psychiatric diagnoses and mortality (157). There are indications that those with a mental condition get lower quality of health care for their somatic conditions (158) and are less likely to comply with treatment for somatic disorders (159) and this may be a contributing factor to the excess mortality.

5.5 WORK ENVIRONMENT

We found that high job demands, job strain and iso-strain were independent risk factors for sick leave due to mental disorders. This finding is in line with other studies (84, 88, 113, 160) and our results add to the current literature by also controlling for familial factors. Our finding that this association was not explained by familial factors is in line with a causal hypothesis, rather than that those with a familial vulnerability for sick leave due to mental disorders report their work environment as having high demands and low control. Sick leave due to work related stress is a well-known public health problem in Sweden. The Social Insurance Agency has found that sick leave is most common in those working in the health care sector and education, and that in these sectors a poor psychosocial work environment is often reported (67). The Swedish Work Environment Authority also reports that health care, social care, public administration, defense, and education has the most reports of social and organizational factors as a cause of reported occupational illnesses (161). The authority has launched new rules on organizational and social work environment, that came into effect on 31 March 2016, in response to the high rates of sick leave and occupational injuries due to work related stress (161). A fair, including, supportive, and empowering leadership has been found to improve mental health and well-being (64). Moreover, flexible time schedules, balance between efforts and rewards, clear goals, the opportunity for influence and education, a permanent contract, a good physical work environment, and control over ones work, also are positive for mental health and well-being (64). However it should be noted that control can be a complex measure as it can be assessed by some as additional demands (87, 162).

5.6 OUTCOMES OF SICK LEAVE DUE TO MENTAL DISORDERS

Familial factors did not significantly influence the association between sick leave due to mental disorders and reoccurring sick leave for the first two years, disability pension, and long-term unemployment. In other words, even though there seems to be a selection into sick leave due to mental disorders depending on genetic vulnerability, familial factors do not seem to significantly influence the effects of such sick leave. There are few previous studies of possible consequences of sick leave taking familial factor into account, but these results are in line with another co-twin study on sick leave, disability pension and mortality (163). A Norwegian heritability study of young adults however, found that both genetic and unique environmental factors, seem to be of importance in the transmission from long term sick leave to disability pension (110).

The reason familial factors would not play a major role in what happens after the sick leave due to mental disorders may be due to external factors such as societal expectations, being of more importance than personal characteristics. This is also supported by the fact that we did not find any large differences in prior unemployment or inpatient care. Stigmatization of persons with mental disorders still exist, even though perhaps more subtle than before, and misconceptions about mental illness may lead to difficulties in finding or maintaining employment after sick leave due to a mental disorder (77). A previous study found that young people with mental disorders had a higher risk of labor market marginalization in terms of not only long-term sick leave and disability pension but also unemployment (164). The concept of a "sick role" has also been described in relation to sick leave and disability pension that describes the social role given to someone sickness absent, that includes the right to be absent from work, that may become permanent (6). It should be noted that in study IV we do not know if the participants "surviving" are in fact employed, only that they are not receiving benefits for disability or sick leave, or are registered as unemployed. Since being registered as unemployed requires actively looking for work and reporting to the Swedish National Employment Office, persons not eligible for unemployment benefits, or with other sources of financial support, may chose not to register.

5.7 SEX DIFFERENCES

The results seem to indicate that likely societal factors are responsible for the sex differences in burnout, mental disorders and sick leave. We did not find any statistically significant sex differences in the heritability of burnout, major depressive disorder or generalized anxiety disorder. However, burnout, major depressive disorder and generalized anxiety disorder were more common among women in line with previous findings (38, 52). Previous meta-analyses found no sex differences in the heritability of major depressive disorder (105) or generalized anxiety disorder (104). However, more recent studies have found that heritability for major depression is somewhat higher in women than men (165, 166) and that the genetic correlation between depression and anxiety was higher for women than men (149). Adjusting for sex did not significantly influence the association between burnout and sick leave. We did find, however, that sick leave due to mental disorders was much more common in women than

men, in line with national statistics (62). Previous research suggests that women and men respond in the same way to work stress (167, 168), and our findings are in line with this, as the association between psychosocial work environment and sick leave due to mental disorders were not significantly affected by adjusting for sex. Women, however, have been found to have higher levels of work strain (168) as well as a greater workload, due to performing the majority of household work and childcare, and women's stress levels has been found to remain elevated also after work, while men's did not (167). Work family conflict, which is more common among women has been found to increase the risk for sick leave (169), though this association may not be independent of familial factors (170).

5.8 METHODOLOGICAL CONSIDERATIONS

5.8.1 The Pines Burnout Measure

The Pines Burnout Measure have been found to equally well distinguish those with and without burnout as the Maslach Burnout Inventory (171). However, The Pines Burnout Measure has been criticized for being unidimensional, and it is indeed mostly correlated with the exhaustion dimension of the Maslash Burnout Inventory (26). Hence, the Pines Burnout Measure could be seen as mainly a measure of exhaustion, rather than that of the original description of burnout (40, 172). However, emotional exhaustion is the central component of burnout (23) and the dimension most related to the diagnostic criteria for exhaustion disorder (Table 1), hence, this measure was appropriate for answering the aims of this thesis. The questions assessing burnout overlap somewhat with diagnostic criteria for depression, such as "fatigue or loss of energy nearly every day" and "depressed mood most of the day, nearly every day" (57) and consequently the measure was highly correlated with major depressive disorder. There is also an overlap with the criteria for anxiety, such as "being easily fatigued" and "difficulty concentrating or mind going blank" and we also found a high correlation between burnout and anxiety. In the additional analysis, I found that those that were on sick leave or disability pension at the time of responding to STAGE, were on average classified as at "risk for burnout" and both those on sick leave or disability pension due to stress-related and other mental disorders, were on average classified as "burned out". Cutoff points have not been validated, but based on this finding the statement that 4.0 is critical to burnout by Pines, seems reasonable (25). It should be noted that the Pines Burnout Measure also enquired about the past year, while the questions regarding depression and anxiety enquired about a two week and a month period over the lifespan respectively. Those with burnout earlier than the past year could not be identified with the available data, even though they may have the genetic predisposition for burnout. This may be why depression and anxiety were correlated to a greater extent with each other, than with burnout in study I, and it may have somewhat overestimated the unique environmental influence on burnout.

5.8.2 Missing data and non-response

STAGE had a response rate of approximately 60%. Sex distribution was approximately equal in the base population (117), however, women are somewhat overrepresented in the STAGE

sample. Moreover, a high proportion of the sample had higher education (44.6 % in study two) compared to the general population 25-64 years old in Sweden (33%) (173). There was also many internal missing data in STAGE, perhaps due to the fact that the questionnaire was so extensive and this was evident in the measures in Study 1. As a consequence, there is a risk of non-response bias that may have affected generalizability of the studies.

5.8.3 Sick-leave register data

Using register data has the benefits of eliminating recall bias and having no loss to follow up. Moreover, a medical certificate with diagnosis and description of work limitations from a physician is required to qualify for sick leave after 7 days. Diagnoses in the MiDAS registry have not been validated, however, a previous study found acceptable validity of the sick-leave diagnoses in an early version of the MiDAS register compared with diagnoses from the medical records in 1991 (174). The diagnostic groups are often very broad and contain many different diagnoses, and since we only had access to three digit ICD-10 codes, we were unable to distinguish among these (50). Moreover, comorbidity is common, we only had access to the primary diagnosis, and differential diagnostics between mental disorders can be difficult at early stages (175). Hence, it should be noted that the diagnostic categories used in this thesis are very broad. In study II, the group somatic conditions contain all diagnoses except for the F-chapter of the ICD-10, and also spells with missing diagnoses. Hence, the category may have some mental diagnoses in it, from the Z-chapter in ICD-10 and due to missing diagnoses. Moreover, we included all spells reimbursed by the Social Insurance Agency, which is normally spells over 14 days. However, shorter spells are present in some circumstances i.e., when a person has a chronic illness and have been approved to get sickness benefit from the Social Insurance Agency from day one, or is unemployed, or on parental leave. There is a risk this may have introduced bias as these groups may be overrepresented.

5.8.4 Assumptions of the biometric twin model

The biometric twin models used in study I and II have some underlying assumptions that need to be further discussed, including random mating, that dizygotic and monozygotic twin pairs share environment to the same extent, that twins are generalizable to the general population for the traits studied and that no epistasis, no gene-environment interactions or correlations are present (140). Moreover, the model only allows inclusion of ether C or D in a sample with twins raised together, an assumption that may lead to an inflated A parameter (140).

Random mating is based on the assumed fact that in the models dizygotic twins share 50% of their segregating genetic material. If people tend to have children with partners that are genetically similar to themselves, siblings and dizygotic twins will share a larger proportion of their genes, which could lead to overestimation of additive genetic effects and an underestimation of dominant genetic effects (103). A study using genome wide data has looked at the actual identity by decent, and found that sibling actually shared 0.498 of their

additive genetic variance (ranging from 0.374-0.617). The non-additive shared genetic variance was 0.248 (ranging from 0.116-0.401). These estimates are very close to the expected 0.5 and 0.25 (176).

The assumption that monozygotic and dizygotic twin pairs share environment to the same extent, has been questioned. It would be possible that monozygotic twins get treated more equally by their families and society compared to dizygotic twins, and also influence each other more. This would lead to an inflated heritability estimate, as shared environment would be interpreted as genetics. However, studies of misclassified twins have found evidence in favor of the equal environment assumption and found that heritability estimates were higher when using genetically confirmed zygosity, compared with self-reported zygosity for behavioral traits including depression. This is the opposite of what would be expected if monozygotic twins were in fact treated more equally (177).

Whether results from twin studies are generalizable to the general population for the traits studied has been debated. The growth of twins in utero is different from singleton pregnancies with compromised growth in the last trimester and the twins often differ in size (101). Moreover, the fact that using reproductive technology more often results in twins may make them differ from singletons. An increased risk of autism, breast and testicular cancer has been seen in twins (101). However, results from twin studies have been found to be generalizable for disability pension due to mental disorders in Sweden (178).

Another assumption is that there is minimal epistasis, gene-environment correlation and interactions for the traits studied (140). Epistasis is the interaction between genes and gene environment correlation reflects that a person to a large degree produces his/her own environment i.e., environments can be found to be heritable because genetic factors influence an individual's exposure to that environment (179). Gene environment interaction means that environment can have different effects on different persons depending on their genetics i.e., genetic factors can make us more or less susceptible to certain environmental factors (179). To give an example, the heritable personality trait performance based self-esteem (PBSE), a self-esteem that is dependent on accomplishments that has been described as the driving force in burnout can be used (41, 180). PBSE may have influenced an individual to choose a workplace with high demands (gene environment correlation) and also made that individual more likely to develop burnout as a result of the high demands, compared to a colleague without PBSE (gene environment interaction). Since this would make monozygotic twins more similar than dizygotic twins this would manifest as genetics in the models, even though the environment would in reality play a large role. This could lead to inflated heritability estimates. Gene-environment correlation and/or interaction, may partly explain why genetic factors were found to completely explain the covariance between burnout and sick leave due to mental disorders in study II. Genetically influenced personality traits, may explain why individuals experiencing burnout remains in a stressful environment and hence later needs sick leave due to a mental disorder, while others change their situation. This relationship between genes and environment can mean that even phenotypes and covariation between

phenotypes that are highly heritable, can be prevented by environmental interventions, which is likely the case for burnout and sick leave due to stress-related mental disorders (179).

5.8.5 Co-twin model

The co-twin method can be seen as the ultimate case control design and has the benefit of adjusting for many unmeasured potential confounders (144). However, there are some potential weaknesses to this design. Statistical power can be reduced in the matched analysis, compared to that of the whole cohort, and this leads to imprecise measurements that leave room for interpretation (181). This problem was encountered in Study III where the co-twin analysis only included less than 3% of the whole sample. Furthermore, using only the discordant pairs may increase confounding by non-shared confounders and increasing measurement error compared with the analysis of the whole sample (182) i.e., selecting out the discordant pairs when the majority of the pairs are concordant for a trait, may lead to missing information and bias. While results should be interpreted with some caution, results from these types of analyses are still a useful tool, especially when used in combination with other study designs (182). A strength in study II is that we performed a biometric twin model to confirm and expand on the results of the co-twin model. In the co-twin model of sick leave due to stress-related mental disorders, estimates are similar for monozygotic twins and dizygotic twins in the regression analysis and not lower for monozygotic, that would be expected based on the results from the Cholesky model. This may be due to gene environment correlation/interaction in the Cholesky model or one of the above mentioned problems with the co-twin model. In Study III an interesting finding was that the ORs were higher in the co-twin analysis, then in that of the whole sample. If familial confounding was present in the form that those with a predisposition for a mental disorder rated their psychosocial work environment as worse than those without such a predisposition we would have expected the ORs to be reduced in the co-twin analyses. Therefore, a possible explanation would be that those with a predisposition for mental disorders actually rated their work environment as better than those without such a predisposition. However, as the sample was greatly reduced in the co-twin model it may also be due to that. In Study IV biases due to selecting out the discordant pairs were unlikely, as the majority of the sample was discordant and having a large sample of discordant pairs was a strength. As the purpose of study four was to follow up what had happened after a spell of sick leave due to a mental disorder, we also chose to only include the complete discordant pairs rather that the whole sample, as in this case it would not have added any information in answering the aim.

5.9 CONCLUSIONS

- Moderate heritability were found for all phenotypes investigated:
    - 37-38% for burnout
    - 45% for major depressive disorder
    - 49% for generalized anxiety disorder
    - 58% for sick leave due to stress-related mental disorders
    - 54% for sick leave due to other mental disorders
- Phenotypic correlations indicate that burnout is strongly correlated with lifetime history of major depressive disorder and generalized anxiety disorder (0.58 and 0.53), and to a lesser extent correlated with future sick leave due to stress-related and other mental disorders (0.26 and 0.30).
- A latent common factor explained the covariation between major depressive disorder, generalized anxiety disorder and burnout. The common facor was influenced to 58% by genetics and to 42% by unique environment.
- Genetic factors was found to be underpinning the association between burnout and future sick leave due to stress-related and other mental disorders.
- Burnout was a significant risk factor for sick leave due to somatic conditions and this modest association did not seem to be influenced by familial factors.
- A poor psychosocial work environment in terms of high job demands, job strain and iso-strain was a risk factor for sick leave due to mental disorders, independent of familial factors and other confounders.
- No independent associations were found between alcohol use, smoking, low physical activity and sick leave due to mental disorders and these health behaviors did not influence the association between a poor psychosocial work environment and sick leave.
- Sick leave due to mental disorders doubled the risk for long term unemployment, independent of familial factors over an up to 8 year follow-up.
- The risk of subsequent sick leave was more than three times higher for those with sick leave due to mental disorders compared with their co-twin for two years after the end of the initial sick leave spell. However, after two years the risk was attenuated and seems to be explained by genetic factors.
- The risk of disability pension was more than 12 times higher for those with sick leave due to mental disorders, compared with their co-twin for a year after the end of the initial sick leave spell, after which they still had more than double the risk.

5.10 FUTURE RESEARCH

Since all phenotypes in this thesis were found to be heritable, twin studies definitely have a place in future studies in the area of burnout and sick leave. However, in future research based on twin data, gene-environment correlation and interaction should be considered. Since we found that burnout was equally associated with sick leave in stress-related as other mental disorders, studies of sick leave due to stress and burnout may benefit from including not only the stress-related, but also other mental diagnoses, including depression and anxiety. Future studies would also benefit from a focus on how depression and anxiety correlates with sick leave and how familial factors impact on this. Moreover, since burnout increased the risk of sick leave due to somatic conditions, and musculoskeletal disorders is the most common somatic sick leave diagnosis, more detailed studies on how burnout affect sick leave due to musculoskeletal disorders would be desirable. Studies on sick leave due to mental disorders and its consequences are still limited even though it is a growing public health problem. The finding that sick leave due to mental disorders was a risk factor for further sick leave, unemployment and disability pension independent of familial factors, warrants attention. Follow up studies on what happens after sick leave due to mental disorders are needed, expanding on different outcomes, return to work and different occupational groups.

6 ACKNOWLEDGEMENTS

These past five years have been quite the journey, and would not have been possible without the help and support from many people and organizations. I would like to start by thanking all the **twins** that took the time respond to STAGE, and made these studies possible.

I would also like to extend a big thank you to the following people:

My main supervisor **Pia Svedberg** for taking me on as a PhD student, for sharing your knowledge with me, and always having an open door to help me solve both big and small problems along the way. I feel that I have received so much more than the basic doctoral education and I very much appreciate the opportunities to attend the best courses on twin methodology around the world, as well as the freedom and support in trying out new ideas.

My co-supervisor **Victoria Blom** for your support and encouragement, sharing your knowledge and expertise in burnout and twin studies, and for all great discussions over the years.

My co-supervisor **Gunnar Bergström** for your thought provoking questions that always made me think more closely on the underlying mechanisms and the bigger picture, and teaching me the importance of Table 1.

All **my colleagues** at the Division of Insurance Medicine, it has been a pleasure to work here. Thank you for interesting conversations about research and life in general, and for always being kind, supportive and available to answer questions. Thank you **Kristina Alexanderson**, for providing a great work- and learning environment, and sharing your expertise in social insurance. I have very much appreciated the input that I got at the manuscript seminars, thank you for being opponents: **Richard Bränström**, **Mo Wang**, **Jurgita Narusyte**, **Pia Kvillemo, Mikael Wiberg**, **Ellenor Mittendorfer-Rutz**, **Syed Rahman** and especially to **Staffan Marklund** for being the opponent at my kappa seminar. I would also like to thank my roommates over the years **Katharina Zetterström**, **Rasmus Elrud** and **Domitilla Di Thiene** for good company. Thank you **Katarina Lönnqvist** and **Annika Evolahti** for much needed administrative support. I would also like to thank the statisticians that have done great work with the register data I used, **Kerstin Nilsson**, **Linnea Kjeldgård** and **Elin Hinas**.

My mentor **Jette Möller** for opening my eyes to the possibility of becoming a PhD student during my master's programme and for support along the way.

My friends and fellow PhD students **Björg Helgadottir**, **Kathleen Bokenberger**, **Charisse Johnson** and **Bojing Liu** for all the good times, good food, travels and discussions. It has been great going through this journey together!

My parents **Gun** and **Jan-Olov** for all of your support, especially after we moved back to Sweden, and helping us out so I could follow my heart and go back to university. My sisters **Åsa** and **Karin** with families for reminding me there is a life outside university, thank you for

your companionship and all the laughter over the years and for being the best sisters one could wish for.

My husband **Hilton**, for leaving everything you knew behind to come live with me in this cold and dark country when I was homesick, and for always believing in me. During this process I also became a mother, and I was so very lucky to get the best children in the world! Thank you to **Matilda** and **Saga** for giving my life purpose and filling it with love. I would also like to thank my little dachshund/oldest child **Lexi**, for dragging me away from the computer out for a walk, where I do some of my best thinking.

I would like to thank the following for **financial support**: the Swedish Research Council for Health, Working Life and Welfare, Karolinska Institutet Doctoral student Funding (KID), the Strategic Research Program in Epidemiology, the Swedish Society of Medicine, AFA Insurance, and Magnus Bergvall Foundation.

The Swedish Twin Registry is supported by Sweden's Department of Higher Education, AstraZeneca, and the Swedish Research Council. The Study of Twin Adults: Genes and Environment (STAGE) was supported by the National Institute of Health, USA, grants [DK 066134] and [CA 085739].

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