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DEPRESSION AND CARDIOVASCULAR DISEASES

Aysha Almas

Karolinska Institutet

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DEPRESSION AND CARDIOVASCULAR DISEASES

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Aysha Almas

Principal Supervisor:
Associate Professor Jette Möller
Karolinska Institutet
Department of Public Health Sciences

Co-supervisor(s):
Professor Yvonne Forsell
Karolinska Institutet
Department of Public Health Sciences

Associate Professor Romaina Iqbal
Aga Khan University
Department of Community Health Sciences

Opponent:
Professor Ingmar Skoog
University of Gothenburg
Department of Psychiatry and Neurochemistry

Examination Board:
Associate Professor Johan Reutfors
Karolinska Institutet
Department of Medicine, Solna

Associate Professor Yvonne von Hausswolff-Juhlin
Karolinska Institutet
Department of Clinical Neuroscience

Professor Eva Swahn
Linköpings University
Department of Medical and Health Sciences

My father Iqbal Ahmed and my mother Safia Khatoon, who taught me that “being educated means being honest and humble”.

ABSTRACT

Background and aim

The concept of depression as a risk factor for cardiovascular diseases (CVD) is now well known. However, weather the severity of depression has a dose response effect on risk of CVD is not known. Also the role of risk factors which might be shared between depression and CVD, their interaction with depression and the combined effect on risk of CVD is still not well understood. For example, high level neuroticism is a risk factor for depression but also for CVD, but the combined effect of depression and high-level neuroticism on risk of CVD is not known. Likewise having comorbid conditions is linked to both depression and CVD, but the combined effect of depression and certain non-cardiovascular morbid conditions on risk of CVD is not known. The role of certain specific genotypes like Catechol-O methyltransferase (COMT) genotype and depression on risk of CVD is also less studied.

The main aim of this PhD thesis is to increase the knowledge on the association between depression and cardiovascular diseases.

Methods and Results

For the purpose of this thesis I used the PART study (acronym in Swedish for: Psykisk hälsa, Arbete och RelaTioner, In English: Physical Health, Work and Relations), a longitudinal study of mental health, work and relations among adults ≥ 20 years of age residing in Stockholm County, Sweden. The study included three data collections, wave 1 (W1) in 1998–2000, wave 2 (W2) in 2001–2003 and wave 3 (W3) in 2010. In total 10,443 individuals were included. Depression was assessed using the Major Depression Inventory (MDI). Severity of depression was assessed using MDI and additionally measuring anxious distress according to DSM-5 (paper I). Neuroticism was assessed by the Swedish Scale of Personality (SSP) for paper II. COMT genotype was measured using saliva from a subsample of the participants (paper III). Non-cardiovascular morbidity was assessed by asking current status of non-cardiovascular morbid conditions (paper IV). All participants from W1 were followed for cardiovascular outcomes through the National Patient register. For study III on genotype all participants from W1 were invited to contribute saliva for DNA

analysis, but only 4349 participated. Logistic regression and Cox regression was used to estimate the risk of CVD.

In study I, I found that depression increased the risk of CVD at different severity levels of depression, and the highest risk was for those suffering from moderate depression. The increased risk was present for both ischemic heart disease and stroke. Also, those who suffered from depression with anxious distress were at higher risk for CVD.

In study II on depression, neuroticism and CVD, I found that those who were depressed and had high level neuroticism were at increased risk of CVD than those depressed with low level of neuroticism. The interaction effect was confirmed by a synergy index > 1.

In study III, the genetic study on the subsample of the PART, I found that those who were depressed and had a high activity COMT Val^{158}Met genotype were at increased risk of CVD compared to those depressed with low activity COMT Val^{158}Met.

In Study IV, those who had depression and non-cardiovascular morbidity were at increased risk for CVD compared to those depressed with no non-cardiovascular morbidity. This risk was present also after accounting for age, gender, socioeconomic status and lifestyle factors. The interaction effect was confirmed by synergy index > 1.

Conclusion

This thesis has overall increased the knowledge on the association between depression and CVD. It further elaborated and created new knowledge on the effect of other factors like personality trait neuroticism, genes and non-cardiovascular morbid conditions on the association between depression and CVD. More studies are required to confirm the biological mechanism in this relation and also design interventions to timely treat depression and other related factors to counter the risk of CVD.

LIST OF SCIENTIFIC PAPERS

I. **Almas A**, Forsell Y, Iqbal R, Janszky I, Moller J. Severity of Depression, Anxious Distress and the Risk of Cardiovascular Disease in a Swedish Population-Based Cohort. PLoS One. 2015 Oct 15; 10(10):e0140742.

II. **Almas A**, Moller J, Iqbal R, Forsell Y. Effect of neuroticism on risk of cardiovascular disease in depressed persons - a Swedish population-based cohort study. BMC Cardiovasc Disord. 2017 Jul 11;17(1):185.

III. **Almas A**, Forsell Y, Millischer V, Moller J, Lavebratt C. Association of Catechol-O-methyltransferase (COMT Val158Met) with future risk of cardiovascular disease in depressed individuals - a Swedish population-based cohort study. BMC Med Genet. 2018 Jul 25;19(1):126.

IV. **Almas A**, Moller J, Iqbal R, Lundin A, Forsell Y. Effect of depression and non-cardiovascular morbidity on the risk of future cardiovascular disease. A population-based cohort study in Sweden. Manuscript

CONTENTS

LIST OF ABBREVIATIONS

CVD	Cardiovascular Diseases
IHD	Ischemic Heart Diseases
MDI	Major Depression Inventory
SSP	Swedish Scale of Personality
COMT	Catechol-O methyltransferase
SI	Synergy Index
ICD -10	National patient register
DSM-5	Diagnostic and Statistical Manual of Mental Disorders

1 BACKGROUND

Depressive disorders are substantial cause of non-fatal burden of diseases (1). Major depression results when depressive moods turn into a chronic, incapacitating disorder interfering with daily life (2). The life-time prevalence of depression worldwide has been reported to vary between 8-12% and about eighty percent have recurrent episodes (3-5). Depression has multiple risk factors including genetics, physical, social and environmental ones (5, 6).

Cardiovascular diseases (CVD) tops the list of the five leading causes of death globally during the last decade (7). Ischaemic heart disease and cerebrovascular disease are jointly responsible for more than 85.1% of all cardiovascular disease deaths in 2016 (8). Globally, deaths from CVD increased by 14.5% between 2006 to 2016 (7). Established risk factors for CVD are high cholesterol, smoking, hypertension, diabetes, abdominal obesity, psychosocial issues, low consumption of fruits and vegetables, hazardous alcohol intake, family history of CVD and lack of physical activity (9).

CVD being the leading cause of death today and depressive disorders being the major cause of non-fatal burden of diseases are of great public health significance. Furthermore, there is evidence that CVD events often are followed by depressive symptoms and that depression is a risk factor for CVD (10, 11). There is emphasis on promoting healthy lifestyle, control of hypertension, diabetes and dyslipidaemia for prevention of CVD both in clinical and public health settings (12-14). However, the concept of focusing on treating depression as a contributor to future CVD is relatively less established. Physicians and cardiologist in general primarily focus on controlling established modifiable risk factors and pay less attention to treatment of depression. The reasons for this disconnect in evidence and practise might be several. Firstly, data on severity of depressive disorders including depression in relation to CVD is lacking. Secondly, shared risk factors and mediators between depression and CVD are not very well studied. There might be some genetic, social, physical or environmental risk factors that are shared between depression and CVD. Thirdly, intervention studies incorporating treatment of depression, in addition to established modifiable risk factors, as intervention to reduce risk of CVD are few and in the initial phase (15).

1.1 DEPRESSIVE DISORDERS

Depressive disorders include disruptive mood disturbance disorder, major depression , persistent depressive disorder , premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, and unspecified depressive disorder (16). These disorders differ in duration, timing, and presumed aetiology.

1.1.1 Major depression

Major depression (or shortly termed as depression) is defined as distinct episodes of at least two weeks' duration (although most episodes last longer) involving clear-cut changes in affect, cognition, and neuro-vegetative functions and inter-episode remissions (17, 18). The mood changes of depression are due to a functional deficiency of the brain monoaminergic transmitters including norepinephrine, 5/hydroxy tryptamine and/or dopamine. This is also referred to as the Monoamine hypothesis.(19) Prevalence rates for single lifetime episode of major depression has been estimated to 6.4% (20). I will be referring major depression as depression in the subsequent text for ease of understanding.

Depression is known as a cause of increased morbidity and has been associated with high health care expenditure, adverse health outcomes, significant functional disability, reduced work capacity and productivity, occupational disability and incident organic disease development (2). Despite these consequences of depression and available effective treatments, a majority of those depressed remain untreated (21). Untreated depression is associated with financial barriers, male gender, ethnic minority and both young and old ages (22-25).

1.2 ASSESMENT OF DEPRESSION

According to Diagnostic and statistical manual of mental health-IV(DSM-IV)and International classification of diseases (ICD-10), five of the following symptoms should be present when making a diagnosis of depression; depressed mood, diminished interest in surroundings , loss of pleasure in all or almost all activities, weight loss or gain , insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, feelings of worthlessness or inappropriate guilt, reduced ability to concentrate, recurrent thoughts of death or suicide (26, 27). At least one of the

symptoms must be either depressed mood, diminished interest or loss of pleasure. The symptom should last at least 2 weeks.

1.2.1 Scales for assessing depression

Choosing the right tool for assessing depression is essential when conducting studies to assess depression on population-based samples. The tools used in general are self-rating scales (screening tools and diagnostic tools) and the gold standard is always in-depth interview (structured or semi structured) by an experienced mental health clinician (28). Self-rating scales are cheaper and therefore are more widely used (29) but tend to be less sensitive in capturing changes in depressive symptoms over time (30).The sensitivity and specificity to diagnose depression for the self-rating scales has been estimated to 94 %(31). Clinically administered tools, on the other hand, are costly, requires additional requirements on clinicians' training and consultation times (32) but clinician administered scales are more sensitive to record change in depressive symptoms over time (30).

The list of instruments available to assess depression is quite exhaustive. Most time tested self-rating tool for assessment of depression in general populations is Beck Depression Inventory (BDI) (33). The most seasoned clinician administered tool for measuring depression is the Hamilton Depression Rating Scale (34). An important two-step instrument to screen and diagnose depression in primary care is the self-administered Patient Health Questionnaire (PHQ) (35).

BDI is a 21 item self-rating scale, based on DSM III(33) This scale was designed to measure the severity of depressive symptoms that a person is experiencing “at that moment“. The BDI has undergone amendments and the latest one is the BDI II (36). However the clinical usefulness of the BDI when covering the DSM-IV symptoms of depression is limited (37). As a result the Major Depression Inventory (MDI), a self-rating scale, was developed by Beck covering both International Classification of Diseases and Related Health Problems and 10th Revision (ICD-10). It was based on the nine DSM-IV symptoms and with marking points from 0 (not present) to 4 (severely present). I will focus on MDI, since studies based in this thesis is based on a population-based sample.

1.3 SEVERITY OF DEPRESSION

The severity of depression, predicts short-term treatment outcomes, probability of recovery, and response to pharmacological treatment (38-40). Severity of depression is measured based on number of symptoms over a 2 weeks period irrespective of the wellbeing or functional impairment.(41, 42) Alternative way of assessing severity of depression is using a categorisation from mild to severe depression. Mild depression is symptoms of depression resulting in only slight functional impairment. Moderate depression is symptoms with functional impairment between 'mild' and 'severe'. Severe depression is symptoms which markedly interferes with routine functioning. It may occur with or without psychotic symptoms (43). Some studies have assessed severity of depression in terms of psychosocial functioning and quality of life (44).

In this thesis the former criteria for assessment of depression severity based on number of symptoms was used. The reason for this is that it is more practical to measure in this way in a large population-based samples and also since it can be self-administered.

Commonly used scales used to assess depression severity include PHQ-9 (45), Hospital Anxiety and Depression Scale (HADS-D)(46) and Hamilton Depression Rating Scale. However, all of these are used in primary care or hospital settings. Overall Depression Severity and Impairment Scale is a 5-item, continuous measure, developed to assess severity of mood disorders and with sub-threshold depressive symptoms (47). However this is more adapted to measure changes in depression status rather than diagnosis. BDI also discusses about severity of depression and categorizes it to mild, moderate and severe depression based on the total scores (48). ICD-10 criteria for diagnosing depression categorizes severity of depression into mild, moderate and severe depression.(26) MDI is a validated diagnostic tool for assessing depression, which also measures severity of depression (49).

Anxious distress

In the DSM-IV, severity of depression is assessed using ‘number of criteria symptoms’, ‘the severity of the symptoms’ and ‘degree of functional disability’. These three specific measures of depressive severity do not correlate well and are not equivalent, for example somebody who has more severe symptoms might still have a high functional level (50). Hence clinical specifier of severity for major depression

has been included in DSM-5. These specifiers are depression with anxious distress, with mixed features, with melancholic features, with atypical features, with psychotic features, with seasonal features, peri-partum and with complete or partial remission

“Anxious distress is defined as the presence of at least two of the following symptoms during most of days during a major depressive episode; feeling keyed up or tense, feeling unusually restless, having difficulty in concentrating because of worry, fear that something awful may happen, feeling that the individual might lose control of himself or herself “(16). Previously “mixed anxiety depressive disorder“ was considered as a separate entity, however reports of test-retest reliability of mixed anxiety depressive disorder found that the diagnosis could not be reliably separated from major depression or generalized anxiety disorder (51). So in DSM-5 “mixed anxiety depressive disorder “was abandoned and anxious distress was introduced as specifier to depression to incorporate common anxious symptoms.

1.3.1 Risk factors of depression

Risk factors of depression have been categorized into genetic and physical, environmental and social risk factors.

Genetic and physical risk factors

Genetic risk factors for depression have been reported in twin and family studies(52) and studies report it to be of more significance in men than in women.(52, 53) Physical risk factors include increasing age (54, 55), being female (56, 57), prior depressive episode (58), suffering from physical medical conditions (59), ethnicity (60), negative affectivity or neuroticism (61) and history of suicide attempts (62) and addictions (63). Genetic and physical risk factors relevant to this thesis are discussed in more detail in section 1.3 later.

Environmental risk factors

Neighborhood or the surrounding environment (64) inappropriate psychosocial work environment (65) , physical trauma(66) are considered as some of the environmental risk factors for depression.

Social risk factors

The social risk factors for depression reported in the literature are childhood adversity (67, 68), stressful life events (69), poor social support and substance abuse (70) and childhood parental loss.(71) Low socioeconomic position is also linked to depression (72).

1.3.1.1 Personality trait Neuroticism and depression

Personality refers to individual differences in characteristic patterns of thinking, feeling and behaving (73). This differentiates persons from each other. Costa has defined five personality traits, called the “Big Five”, which are broad areas or dimensions of personality that can be used to describe human personality (74). The domains are called openness, conscientiousness, extraversion, agreeableness and neuroticism. *Openness to experience* is the personality trait which has likes art, sentiment, adventure, uncommon ideas, curiosity, and variety of experience. *Conscientiousness* is a personality trait referring to a tendency to show self-discipline, act with responsibility, and aim for accomplishment; planned behavior rather than impulsive; organized, and dependable. *Extraversion* is the personality trait which has energy, positive emotions, urgency, decisiveness, sociability and the tendency to seek stimulation in others, and talkativeness. *Agreeableness* is the personality trait that tends to be compassionate and helpful and not doubtful and opposed towards others. It is also a measure of ones' trusting and helpful nature, and whether a person is generally well tempered or not. *Neuroticism* is a personality trait with the tendency to experience unpleasant emotions easily, like anger, anxiety, depression or vulnerability. Neuroticism also refers to the “degree of emotional stability and impulse control.”

Specific traits in personality like neuroticism increases the risk of developing depression. In a secondary data analysis on 1000 people, high level neuroticism was a significant prospective predictor of depression (75). In a study conducted on 270 adolescents, development of personality trait neuroticism with age was associated with negatively toned emotional experience and depressive and anxiety disorders in young adulthood.(76, 77) Among all five personality traits mentioned above, neuroticism is strongly associated with depression (61).

1.3.1.2 Genetics and depression

There are several well established genetic associations to depression in studies of animal models and culturally and ethnically homogeneous patient materials (52). Studies on Twins suggest a heritability of 40-50%, and family studies indicate a two- to threefold increase in risk of developing depression among first-degree relatives (78). In a large national sample, the heritability of major depression was similar when estimated from twin and full/half-sibling designs (79). So far, most genetic studies on depression have focused on genes regulating the serotonergic and dopaminergic neurotransmission (80).

Dopamine pathway in genetics and depression

Deficiency of dopamine in specific areas of the brain, called the mesolimbic dopamine system or the brain reward system, contributes to the expression of depression (81). Increased dopamine, produced in synaptic clefts in these areas, have been shown to be metabolized by dopamine transporters (DAT) or degraded by monoamine oxidase A (MAOA) or *Catechol-O-Methyltransferase (COMT)* (82). *COMT* metabolizes not only dopamine but also other catechol amines and sex steroids, like catechol oestrogens and dietary polyphenols. *COMT* activity is dependent on genetic variations in the *COMT* gene. *COMT* contains a functional single nucleotide polymorphism (SNP) – rs4680 – that codes for a replacement of methionine (Met) for valine (Val) at codon 158. The Met allele has less enzymatic activity compared to the Val allele (83). The Val/Val genotype is associated with about 40% more effective degradation of dopamine compared to the Met/Met genotype (84). This might be a possible link in between depression and the specific genotype controlling the dopamine metabolism.

1.3.1.3 Comorbidity and depression

Comorbidity is referred to as the presence of additional diseases in relation to an index disease in a person (85). Depression, while being a disabling condition itself, when coexists with co-occurring medical condition, makes treatment and recovery difficult (86). Chronic illness increases the risk of depression. Depression is 2 times more common among patients with diabetes mellitus, coronary artery disease, HIV infection, and stroke than among patients free of chronic illness (87). Additionally depression increases the risk of type 2 diabetes (88) and coronary artery disease

(89). Hence the relationship between depression and other acute or chronic medical conditions can be bi-directional and it is often difficult to establish clear temporality.

Non-cardiovascular morbidity is a relatively new term, defined as comorbidities not considered as independent risk factors for CVD (90). Non-cardiovascular morbidities generally include respiratory, endocrine (excluding diabetes), nutritional, renal, hematopoietic, neurological as well as musculoskeletal conditions (91). Coexistence of depression and comorbid conditions often leads to overexpression of somatic symptoms, like pain, thus complicating the treatment (92). It is also associated with reduced quality of life, higher costs, and worse health outcomes and requires extensive coordination across various health services (59, 93).

1.4 CARDIOVASCULAR DISEASES

CVD are generally stated to as conditions that involve narrowed or blocked (thrombosis) blood vessels that can lead to ischemic heart disease (IHD) (myocardial infarction, angina) or stroke. This prevents blood from reaching to the heart or brain. The most common reason is a pooling of fatty deposits on the inner walls of the blood vessels which forms the thrombus (clot) which blocks the arteries. Strokes can be caused by blood clots or bleeding from a blood vessel in the brain (72). Eighteen million deaths annually is attributed to cardiovascular diseases worldwide (94). The incidence of major cardiovascular events has been reported to be highest in low-income countries, despite the fact that these countries have lower risk-factor burden (95).

Both myocardial infarctions and strokes contribute to the global burden of CVD. The global burden of IHD increased by 29 million disability-adjusted life-years (29% increases) from1990-2010 (96). The burden of both ischemic and haemorrhagic stroke has increased significantly from 1990-2010 in terms of an increased absolute number of people with incident stroke, number of deaths, and number of disability in life years lost (97). It is this fatal nature of these specific CVDs (acute myocardial infraction, unstable angina and stroke) that they were included as the main outcome in all studies of this thesis.

1.4.1 Acute myocardial infarction and unstable angina

Acute myocardial infarction is defined as an event of myocardial necrosis caused by an unstable ruptured plaque. Clinically it is diagnosed and assessed on the basis of

symptoms like chest pain or heaviness, electrocardiogram (ECG), biochemical testing, invasive and noninvasive imaging (98). Unstable angina is defined as myocardial ischemia at rest or minimal exertion in the absence of death of heart muscle (99). Total deaths from ischemic heart disease rose by 19.0% increasing from 7.96 million deaths in 2006 to 9.48 million deaths in 2016, which mainly accounts for the overall increase in total deaths from cardiovascular diseases (7).

1.4.2 Stroke

Stroke is manifested as a neurological deficit attributed to an acute focal injury in the brain parenchyma due to vascular thrombosis, including cerebral infarction (due to arterial thrombosis), intracerebral hemorrhage, and subarachnoid hemorrhage, and is a major cause of disability and death globally (100). Stroke is the second most common cause of deaths 11.8% of all deaths worldwide (after ischemic heart diseases) (101).

1.4.3 Risk factors for CVD

Several risk factors for cardiovascular diseases have been reported in the literature. Some of them have been classified into genetic, cardio-metabolic, environmental /Psychosocial/Physical and lifestyle risk factors.

Genetic predisposition

Genetics or family history of CVD are important risk factors for CVD. CVD of early onset, have a genetic basis and a host of genes have been identified in connection with atherosclerotic CVD (102). Having at least one parent suffering from CVD doubles the 8-year risk of CVD among men and by 70% among women (103).

Cardio-metabolic risk factors

Cardio-metabolic risk factors include obesity, diabetes, high cholesterol and high blood pressure (9, 104). Hypertension is the leading risk factor for CVD (7). Obesity is associated with increased risk of CVD and also worsens the CVD risk factors like hypertension and high cholesterol.(105) Diabetes is also a major risk factor for CVD and almost half of diabetic patients die due to heart disease (106). Hypercholesterolemia with an increased serum low-density lipoprotein (LDL) cholesterol is a major risk factor for CVD (107).

Environmental /Psychosocial/Physical

Apart from the physical and behavioural risk factors, environmental risk factors, on which an individual has little control are also present. These include air pollution leading to deaths from ischaemic heart disease and stroke (108), lack of space for physical activity (109), dietary regulations on availability of certain high salt food (110). Socioeconomic status has strong inverse relation with CVD (111)The psychosocial risk factors include the following;, inappropriate psychosocial work environment (112), neuroticism (113) and depression (114). The physical risk factors include comorbid conditions (115) and physical trauma (116).

1.4.3.1 Lifestyle

Physical inactivity, hazardous alcohol use, inadequate nutrition (inadequate fruits and vegetable intake) and smoking are the lifestyle behaviors that increase the risk of CVD (8, 117). Physical activities of both moderate and vigorous intensity are associated with reduced risk of CVD (118). Light-to-moderate alcohol consumption has been shown to be linearly associated with a decreased risk of acute myocardial infarction.(119) Diet including high-fat and high salt diet, less fruit and vegetable intake and smoking are also important risk factor for CVD (95).

1.4.4 Assessment of CVD

Assessment of cardiovascular disease can be done based on self-reports(120). Clinical diagnostic criteria for ischemic heart diseases include symptoms of chest pain, electrocardiogram and troponin I blood test (121). Additionally, specialized diagnostic investigations like myocardial perfusion imaging, coronary angiography and echocardiography (rest and during exercise) are also used for assessment of ischemic heart disease and acute myocardial infraction (122). Clinical diagnostic criteria for assessment for stroke is sudden focal loss function of any body part (100). Additionally computed tomography and magnetic resonance imaging of the brain are specialized diagnostic investigations used for assessment for stroke (123).

Patient registers from health care facilities are also used for assessment of CVD. In this thesis the Swedish National Patient Register (NPR) was used for evaluation of CVD. The NPR was founded in 1964 and complete national coverage started in 1987 (coding adapted from the WHO ICD classification system). Currently, more than 99% of all somatic (including surgery) and psychiatric hospital discharges are

registered in it (124). It was validated by the National Board of Health and Welfare revealed that 85-95% of all diagnoses are valid (125, 126). The validity of diagnosis of myocardial infarctions by NPR is 90.3%. It is mandatory for all physicians to report data on patients to the NPR (excluding primary care). Each hospital discharge is linked to an individual's personal identity number (127).Missing primary (main) diagnosis in NPR is 0.8% for somatic care, 2.4% for geriatric care, 3.1% for psychiatric care and 0.5% of general surgery which is quite low. (126). The Swedish cause of death register has been electronically available from 1952 (128).The cause of death register has validity of 77% for cause of death when compared to the cause of death expected based on case summaries.(129)

1.5 DEPRESSION AND CVD

As mentioned in the previous section, depression is one of the risk factors for CVD. The reason that this relation is of importance is that while CVD is linked to mortality, depression is linked to disability (1, 7). The existence of depression and later CVD in the same individual is therefore associated with worse health outcome. A meta-analysis including 28 studies on 80,000 patients concluded that depression was an independent risk factor for CVD (10). In the past two decades, some prospective studies have found a relatively strong association between depression and subsequent events of cardiovascular disease (CVD) in initially CVD free populations.(130, 131) In a large retrospective cohort study on 4.6 million Danish persons from the general population; adjusted risks of cardiac hospital admissions and death were significantly increased to 68% in persons with hospital admissions due to depression.(132). Similarly in another cohort study on elderly community dwelling individuals apathy, but not depression, was found to be a strong, independent risk factor for incident CVD.(133)

1.5.1 Depression and Acute myocardial infarction (and unstable angina)

The INTERHEART study, a large multicentre case–control examination of modifiable risk factors for myocardial infarction, found that psychosocial factors (such as locus of control, perceived stress, and life events) results in a 2.7-fold increased risk of acute myocardial infarction (AMI) (9). A meta-analysis concludes that depression is independently associated with increased risk of acute myocardial infarction (134). In contrast Rahman et al reported, analysing a cohort study on 36 654 elderly Swedes

showed a significant association of untreated depression with ischemic stroke but not with coronary heart disease (135).

1.5.2 Depression and stroke

Depression has also been associated with stroke (136). A meta-analysis including 28 prospective cohort studies on 317,540 participants concluded that depression increases the risk of stroke morbidity and mortality (137). A recent longitudinal study reported depression as being a risk factor for developing stroke among middle aged women (138).

1.6 POTENTIAL MECHANISMS OF DEPRESSION LEADING TO CARDIOVASCULAR DISEASE

The notion of bio-behavioural model to explain the relationship between depression and CVD is gaining support in the literature (139). This model categorises the mechanisms into biological and behavioural mediators.(11) (Figure 1. Relationship between depression and cardiovascular disorders).

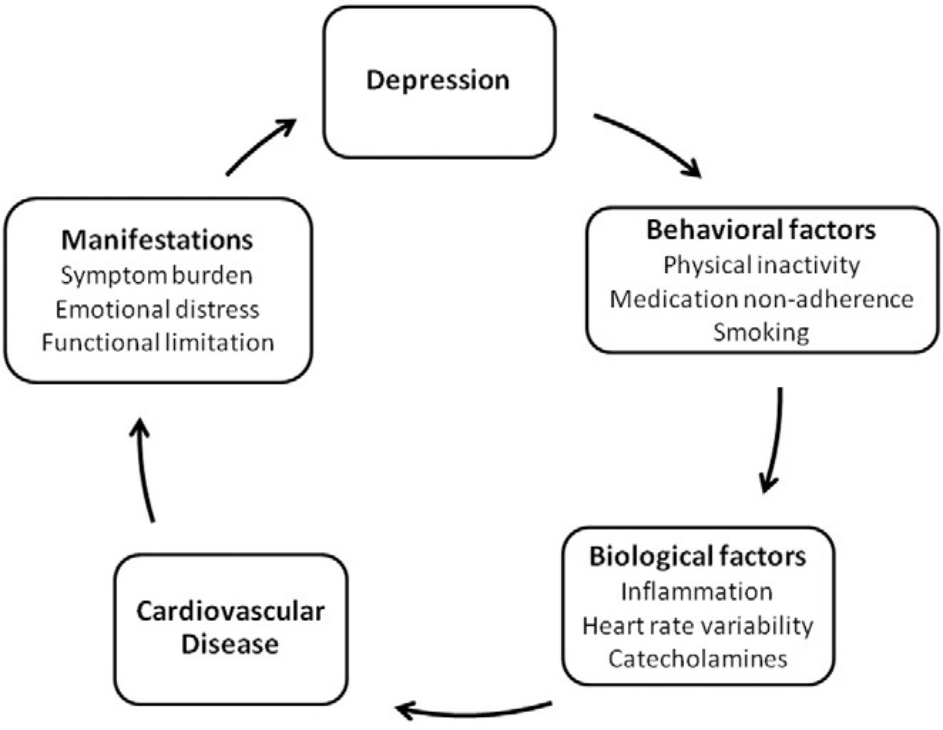


Figure 1. Relationship between depression and cardiovascular disorders. (Elderon et al, 2013)

1.6.1 Biological Mechanisms

Among the Biological dysregulation mechanisms some specific pathways have been reported. These include

(a) Metabolic dysregulation: The dysregulation of metabolic factors including central obesity, increased blood sugar, high blood pressure, increased triglycerides and decreased HDL cholesterol contributes to the pathophysiology of depression leading to CVD. There is consistent evidence associating depression and obesity-related components, i.e. central obesity, low HDL cholesterol, hypertriglyceridemia (139, 140). These factors are also likely to be genetically determined.

(b) Immuno-inflammatory dysregulation: Depression is associated with dysregulated inflammation; an immune response that derives from activation of the innate immune system including proinflammatory cytokines(interleukin (IL)-1, IL-6) and tumour necrosis factor (TNF)-α) produced within innate immune cells in response to immunologic challenge (140). Also increased platelet stimulation and endothelial dysfunction in blood vessels is reported as a potential pathophysiological pathway linking depression and CVD (141).

(c) Autonomic dysregulation: The concept that stress response during natural disasters, terror attacks (142)or soccer matches have been associated with increased risk of acute cardiovascular events. Such stressful situations lead to activation of cardiac sympathetic nerves (143). There is evidence of hyper sympathetic/hypo vagal state among depressed persons. Autonomic dysregulation results in sympathetic stimulation leading to tachycardia, blood pressure liability and tendencies toward hypertension (144). Studies have also reported that in patients with major depression, there is noradrenalin spill over resulting in increased sympathetic activity (145). This increased sympathetic activity further leads to hypertension which is an established risk factor of CVD (146).

(d) Hypothalamic-pituitary-adrenal axis activity: Chronic stress is professed by the cortex of the brain and conveyed to the hypothalamus, where corticotrophin-releasing hormone (CRH) resulting in release of cortisol into the blood (11, 147). This in turn increases the stress response and blood pressure.

1.6.2 Behavioural mechanisms

The behavioural mechanism can be explained by the fact that depressed people have more often have unhealthy life style behaviours, i.e. are more likely to smoke,

drink hazardous amounts of alcohol, eat an high cholesterol diet and to be less physically active (148, 149). Additionally there is a higher likelihood for non-adherence to medications (e.g. for control of hypertension, diabetes) compared to their non-depressed counterparts, thus further worsening of the CVD risk factors and leading to CVD(150). Certain specific personality types like neuroticism might be at more risk for medication non adherence and this might be a contributory factor (151).

1.7 KNOWLEDGE GAPS

There is support for depression linked to an increased risk for CVD. Some risk factors are shared between depression and CVD for example genes, socioeconomic status, psychosocial work environment, personality trait like neuroticism, comorbid conditions. However, whether coexistence of these individual risk factors with depression (like high level neuroticism or COMT Val/Met,) increases risk of CVD is still a point of debate. Also it would be useful to understand what underlying behavioural or biological mechanism exists in the interaction of depression with other risk factors leading to CVD. It is important to address these gaps as both depression and CVD constitutes a large burden of diseases today, and in order to prevent or treat them a clearer understanding of the interacting risk factors and their mechanisms is essential.

1.7.1 Severity of depression and CVD

Since depression is a risk factor for CVD, it is therefore postulated that the more the degree of depression (number of symptoms of depression), the higher the risk of CVD might be. The dose-response connection between depression and future risk of CVD has not been well studied. In the Nova Scotia Health Survey on 1302 participants, independent and an incremental association between depression and incident CHD was detected in a small population-based sample over a 4-year period (152). In the Netherlands Study of Depression and Anxiety involving 2510 participants, a dose–response association was found for severity of symptoms with CVD (153). Holt et al further reported that the association between depression and cardiovascular diseases was dependent of the severity of depression at baseline (154). However, these studies are based on patients from hospital or clinic settings. Hence whether severity level of depression increases risk of CVD in population-based samples is still not known. Additionally, the role of anxious distress which is a

clinical specifier for severity of depression has not been assessed with regard to risk of CVD.

1.7.2 Depression, high level neuroticism and cardiovascular diseases.

Personality traits , mainly neuroticism may result in psychosocial stress leading to elevated blood pressure, atherosclerosis, and other physiological risk factors (155). High level neuroticism (or high negative affectivity) is associated with cardiovascular outcomes (156). In the British Health and Lifestyle Survey, higher neuroticism was associated with higher risk of coronary heart disease mortality but not with stroke mortality (157). The same cohort was followed up again after 5 years and high neuroticism was a risk factor for cardiovascular mortality in women with low socioeconomic status , whereas in women with higher socio economic status it was protective (158, 159). Pooled analysis from three cohort studies; the Health and Retirement Study, the Wisconsin Longitudinal Study graduate and the Sibling samples (n=24,543) have been included in a study by Jokela et al (113). This study concluded that high level neuroticism was a risk factor for coronary heart disease mortality but not for stroke mortality. Hence whether high level of neuroticism increases risk of CVD in depressed patients is still under debate.

1.7.3 Depression, High COMT Val^{158}Met, and CVD

COMT Val^{158}Met is of interest in the relation between depression and CVD, as it focuses mainly on the catecholamine and dopamine, which are also the essential molecules involved in the pathogenesis of cardiovascular diseases. Previous studies revealed that there is an association between COMT Val158Met and depression in men and also that COMT Val^{158}Met interact with environmental factors on the risk of depression (160). Studies are lacking on the association between COMT Val^{158}Met and cardio-metabolic factors. In one study low activity COMT genotype was shown to be protective for myocardial infarction (161). Another study reported that a low activity COMT genotype Val^{158}Met, was associated with CVD and abdominal obesity in men (162). Hence, whether high COMT activity genotype Val158Met in depressed patients contributes further to an increased risk of developing cardiovascular disorders is still not known.

1.7.4 Depression, non-cardiovascular morbidity and CVD

The interacting pathophysiology of diseases within an individual, complicating diagnosis and treatment of people with multiple comorbid conditions is challenging (163). Also care of such patients become difficult by the physicians and family (164). So far most clinical practice guidelines focus on care of specific disorders. Recent literature suggests that multiple comorbid conditions is not only a problem of elderly patients, but has also become prevalent in non-geriatric populations (165). Number of comorbid conditions and more importantly non-cardiovascular morbidity, have been reported to increase risk of CVD (specifically heart failure) and has been considered an important marker of prognosis in patients with heart failure.(166, 167) Non-cardiovascular morbidity have also been linked to increased risk of heart diseases(168). The effect of coexistence of depression and non-cardiovascular morbidity on the risk of CVD, has to our knowledge been paid less attention. We could find one study by Atlantis et al concluding that the association between depression and CVD mortality is partially mediated by comorbid conditions, as well as unhealthy lifestyle behaviors (169).

2 MAIN AIM AND RESEARCH QUESTIONS

The main aim of the PhD thesis is to increase the knowledge on the association between depression and cardiovascular diseases. This will be achieved by answering the following research questions:

1. Is there effect of severity of depression and anxious distress on the association between depression and cardiovascular diseases?

2. Is there effect of neuroticism on the association between depression and cardiovascular diseases?

3. Is there effect of COMT Val158Met polymorphism on the association between depression and cardiovascular diseases?

4. Is there effect of non-cardiovascular morbidity on the association between depression and cardiovascular diseases?

3 MATERIALS AND METHODS

3.1 STUDY DESIGN AND SETTING

Data for this thesis was derived from a longitudinal cohort study- the PART study - (In Swedish short for: Psykisk hälsa, Arbete och RelaTioner). The PART study is a large longitudinal population based study on risk and protective factors for mental health, among adult people residing in the Stockholm County, Sweden.(170) It includes three waves: wave 1 (W1) with data collection in 1998-2000, wave 2 (W2) in 2001-2003 and wave 3 (W3) in 2010. For this thesis, W1 and W2 were used for assessment of depression. Participants were followed for CVD outcomes in W3 (Study I), National Patient register (2001-2014) and the cause of death register (2001-2014). (124), (128) In Study I, CVD was assessed using W3 data in addition to the National Patient register (2008-2011) as data, at time of analyses, from the register was available only during 2008-2011(Figure II.Schematic overview of the subjects from the PART study included in the sub-studies in the thesis.)

3.1.1 Study Participants

Inclusion criteria

1) Being a Swedish citizen residing in Stockholm County. Only Swedish citizens were chosen to alleviate the possibility of linguistic difficulties.

2) Adults aged $\geq$ 20 years of age were chosen since the PART study focused primarily on those who belonged to the wage-earning age range.

Exclusion criteria

Those who were living in remote municipalities with more than one hour travelling time to the research center.

3.1.2 Waves of the PART study

Wave 1: In 1998-2000, the population of Stockholm County full filling the sampling criteria were 858000.The PART study sample, included 19,744 adult individuals $\geq$ 20 years of age registered in the Stockholm County and randomly selected from the Population register of the Stockholm County. Only 19,457 could be reached due to address issues. Among the latter, 10,443 individuals responded to the questionnaire at wave 1 (53% of the intended sample). Non-response analyses were done by using available administrative and health registers. Of those who responded, data

was analyzed for 10341 participants. Male gender, less than 50 years of age, low income, low educational level, living alone and country of birth outside the Nordic countries were strong elements of non-participation (171). However, associations for all hospital discharge psychiatric diagnoses were similar among participants and non-participants when related to gender, age, income, residential status, education and country of origin.

Wave 2: All participants who participated in wave 1 received a second, almost identical questionnaire three years later. The participation rate at this follow-up phase was 83% (n= 8,622). Reasons for non-response was like those in W1 (172).

Wave 3: All participants who participated in wave 2 received a third, almost identical questionnaire seven to eight years after they had answered the second one. The participation rate at the third follow-up phase was 61% (n= 5,228).

DNA collection wave (2006-2007 and 2010-2011): All participants from W1 (n=10443) were invited to participate in the DNA collection wave to contribute their saliva for DNA analysis. In total 4349 (41%) participated. The reasons for non-participation have been reported to be mainly due to lack of personal relevance of DNA contribution and uneasiness related to DNA usage (173).

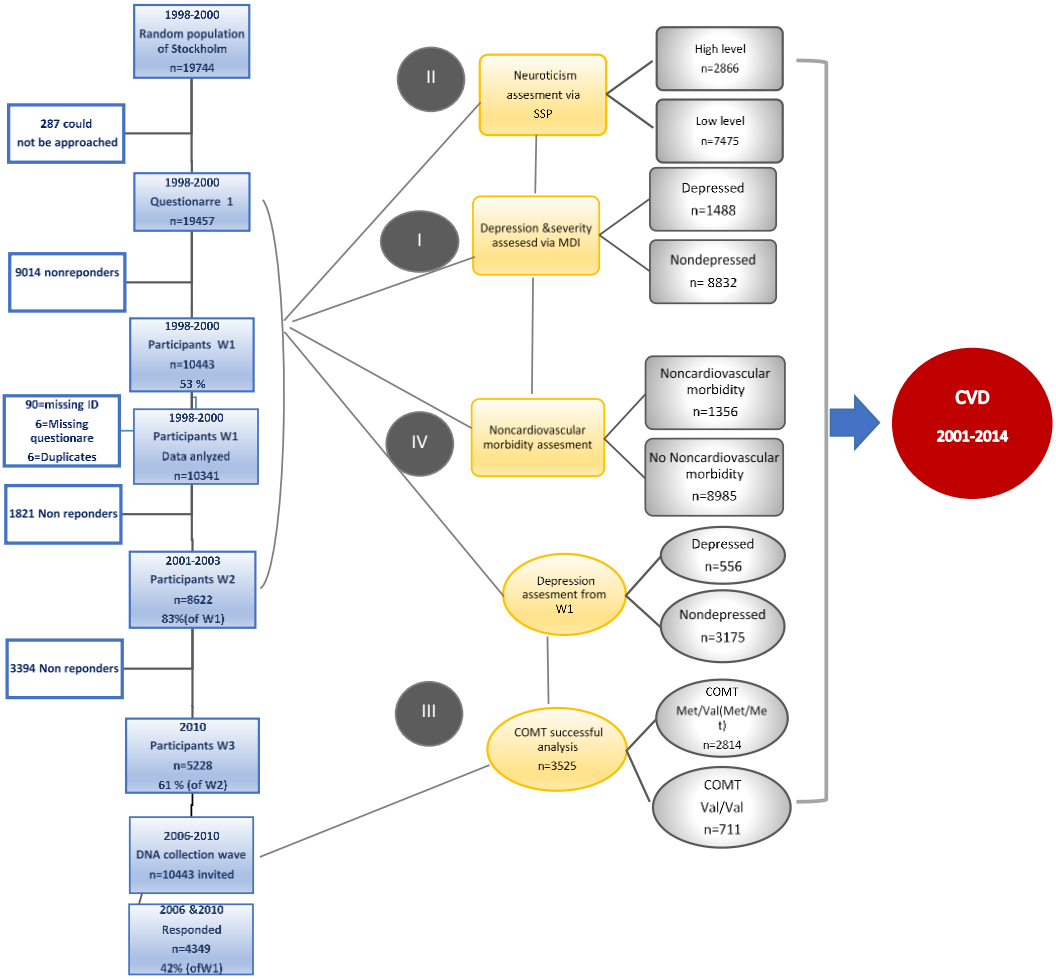


Figure II.Schematic overview of the subjects from the PART study included in the sub-studies in the thesis.

3.2 ETHICAL CONSIDERATIONS

The standard principles of ethics according to the Helsinki declaration were considered and applied to the studies of this thesis. All participants received a detailed pamphlet with instructions about the PART study. Informed consent was taken keeping in mind the principle of autonomy for all participants and it was stated that the participation was voluntary and could be ended anytime. Confidentiality was maintained among participants, so that none of the participants were aware about any information of the other participant. This is necessary as each participant has a right of privacy for his/her personal or health related information. The ethical problem that was encountered was that some participants were not aware of the fact that they were depressed. All persons who revealed that they had suicidal thoughts more than half of the time during the last two weeks was called by the research staff. If needed they were informed about available care, some were offered a visit and talk to one of the psychiatrists in the research team. Research staff was also available by phone and email throughout the study if the participants wanted. At the end of the questionnaire there was free space for comments from the participants. These were all read and in case something alarming was written the participant was contacted, e.g. one participant wrote about sexual abuse another about physical abuse. In order to decrease the rate of internal missing data all participants who did not answer all the questions were contacted. Following the principle of beneficence to the participants, they were then offered to be referred to a psychiatrist.

The studies were approved by the Ethical review board at Karolinska Institutet, Stockholm (96-260, 01-218, 03-302, 2009/880-31, 2012/808-32, 96-260, 97-313, 01-218, 03-302, 2004-528/3, 2009/880-31, and 2012/808-32).

3.3 EXPOSURES

3.3.1 Depression

Major depression inventory (MDI)

Major depression inventory (MDI) was used for assessment of depression. It is a self-rating scale, shown to have high validity both in clinical and non-clinical samples.(174, 175). (See Appendix A for MDI scoring key and instructions). Validity studies of the MDI have been done in Swedish population (176), in clinical settings in different European countries.(41, 49, 177) The sensitivity of MDI was 0.78 and the specificity was 0.78 in a study based on wave 1 of PART.(176) MDI

has shown the highest coefficient of homogeneity when compared to BDI and HAM-D –Hamilton Depression Rating Scale (178).

Depressive symptoms during the past 2 weeks were assessed with a slightly modified version of the MDI for the PART study. To make the PART scale in accordance with criteria of a major depressive episode in DSM-IV, some symptom questions were modified or added, i.e. the question “Have you felt either very restless or rather subdued” was divided into two separate questions: “Have you had trouble sleeping at night” and ”Have you suffered from reduced appetite” were supplemented by the questions ”Have you needed to sleep more than usual” and ”Have you had increased appetite or increased in weight recently”. When analyzing the data the questions on sleep and appetite was considered in combination. One question was added: “Have you felt as if you wanted to take your life”. Moreover, also questions on severity of social impairment due to the symptoms and duration of the symptoms were added. The full PART instrument was used to screen for any symptoms of depression while one of the questions was also used to screen specifically for suicidal thoughts. The MDI includes 10 item questions (question 8 and 10 have 2 sub questions a and b). For items 8 and 10, response alternative a or b with the highest score is considered. Each item has 5 response categories; all the time (5), most of the time (4), slightly more than half of the time (3), slightly less than half of the time (2), some of the time or at no time (1). For simplification the items were dichotomized to indicate the presence (=1) or absence (=0) of each of the symptoms. The first three items of MDI are considered present for answer categories from 4 to 5 (i.e., most of the time, all the time). For the remaining items (items 4–10, response categories from 3–5 (i.e., more than half of the time, most of the time and all the time) are included when scoring the symptoms as being present. The MDI is used both as a diagnostic instrument with the algorithms leading to the DSM-IV or ICD-10 categories ‘major ‘or ‘moderate to severe’ depression, and as a measuring instrument in which the total score is a sufficient statistic (49). Assessment of depression was based on responses in both W1 and W2, and the wave with highest score was used to determine depression and severity of depression.

3.3.2 Severity of Depression

Based on total score of MDI severity of depression was assessed. The 10 items of MDI are added up, to a mathematical score ranging from 0-50 (49). Mild depression

was defined as a total score of 20-24, moderate depression; 25-29 and severe depression ≥30. Those scoring < 20 were considered as non-depressed.

3.3.3 Anxious distress

Concomitant anxious distress was used as a specifier of severity of depression according to DSM-5(17).Anxious distress is considered as a specifier of depression severity according to DSM –V and was defined according to the presence of at least two of the following symptoms;" During the previous two weeks: feeling keyed up or tense, feeling unusually restless, difficulty in concentrating because of worry, fear that something awful might happen and fear of losing self-control." Each symptom was assessed using a 5- or 6-point Likert scale, and, for simplicity, the response alternatives were merged as yes or no, and rated according to DSM-5 number of symptoms (no anxious distress = none or one symptom; mild anxious distress = two symptoms; moderate anxious distress = three symptoms; and moderate to severe anxious distress = four to five symptoms) (179). (See appendix B for DSM-5 criteria for anxious distress and corresponding questions used from scales in mental health in the PART study to assess anxious distress.)

3.3.4 Neuroticism

The Swedish universities Scales of Personality (SSP) was used to assess neuroticism (paper II) (See appendix C for the Swedish scale of personality reflecting neuroticism, mean and T score) (180). SSP is an advanced and composite version of the neo personality inventory which originally comprised of 240 questions to assess the Big five aspects of personality (74) and the Karolinska Scales of Personality (KSP) inventory comprised of 135 items.(181) SSP is a revised, condensed, advanced and psychometrically evaluated version of the Karolinska Scales of Personality (KSP).(180). The SSP inventory consists of 91 items grouped into 13 different scales (See Table 1 for a list of scales in SSP).

Table 1. List of the 13 SSP scales

Scale label
Somatic Trait Anxiety
Psychic Trait Anxiety
Stress Susceptibility
Lack of Assertiveness
Impulsiveness
Adventure Seeking
Detachment
Social Desirability
Embitterment
Trait Irritability
Mistrust
Verbal Trait Aggression
Physical Trait Aggression

Scoring of SSP

Each of the 91 items is given as a statement with a four-point response format, ranging from 1 to 4, 1 point for the" disagree" and so on to 4 points for the "agree". It has been demonstrated that a four-point response format gives better psychometric properties than a dichotomous format. The reported Cronbach's alpha coefficient for internal consistency of SSP ranges from 0.59 to 0.84, and the mean inter-item correlations ranges from 0.17 to 0.43. Based on this the responses personality facets were grouped into 3 main traits was done.(180) Three derived factors which also correlate with the personality theories are (1) neuroticism (2) aggressiveness and (3) extraversion factor. In this study factor 1 indicating neuroticism was used. Factor 1 is mainly comprised of 3 scales assessing broad and narrow traits of neuroticism including:

- Somatic trait Anxiety
- Stress Susceptibility
- Embitterment.

High versus low level Neuroticism

Scores for neuroticism was divided into tertile; cut-off levels at 33.3 and 66.6; lowest tertile ≤ 33.4, middle tertile ranging between 33.5to 66.6 and highest tertile $\underline{>}$66.6. Scores at 66.6 tertile and below were considered as low levels of neuroticism and > 66.6 tertile as high level neuroticism. This cut-off was used to capture those scoring higher in a separate category. Low-level neuroticism was used as reference group in the analysis.

3.3.5 COMT Val^{158}Met

DNA was collected using a self-administered whole-saliva DNA sample collection kit (Oragene, DNA Genotek Inc., Ottawa, Canada) sent to the participants' homes. Saliva was obtained from participants and genomic DNA was extracted using Oragene Purifier. The COMT Val^{158}Met (rs4680) genotype was successfully obtained for 3731 persons (91%) using TaqMan SNP genotyping assays applying an ABI 7900 HT instrument (Applied Bio systems, Foster City, CA).(182) Val/Val (G/G) was considered as the, at risk allele in accordance with previous studies (161, 183) and Met/Met (A/A) or Met/Val (A/G) was used as reference.

3.3.6 Non-cardiovascular morbidity

Non-cardiovascular conditions were based on self-reports to the following questions (a) Are you currently treated for a disease (e.g. peptic ulcer disease) (85). The same question was asked for each of the following diseases; current occurrence of neurological disorders, endocrinological disorders, respiratory disorders, gastrointestinal disorders (dyspepsia or bowel or liver), kidney and urinary tract disorders, genital disorders, serious infections, tumors (benign or malignant), rheumatologic disorders, other heart diseases(other than ischemic heart disease) skin disorders and psychiatric disorders (other than depression).Those who answered yes to any of the above diseases were considered to have non-cardiovascular morbidity.

3.4 OUTCOME

Acute myocardial infarction, unstable angina (including hypertensive heart disease) and stroke were used for assessing the CVD outcomes for all four studies and the outcome was then linked to the PART data from W1 and W2. Also, for the specific studies in this thesis, those who reported current or a history of myocardial infarction or stroke in wave 1 were excluded to ensure a CVD free population at time of follow

3.4.1 Study 1

For study I, CVD outcomes were based on NPR or self-reports. At time of analyzing paper I, register data was available for 2008-2011. Self-reports on CVD was used as reported in the health status questions in W3.” Are you currently or have you previously been on treatment for angina pectoris or have you received this diagnosis from a physician? “Corresponding questions were asked for myocardial infarction, high blood pressure and stroke. The following hospital discharge diagnoses (main and secondary) were derived from the NPR and coded according to ICD10: ischemic/hypertensive heart disease; hypertensive diseases (ICD-10: I11-13), ischemic heart diseases (I20-25), heart failure (I50), other peripheral vascular diseases, embolism and thrombosis (I73-74) and stroke (I60-67 and I69).

3.4.2 Study II, III and IV

Participants were followed in the NPR for CVD outcomes from 2001-2014. The endpoints considered were: time of CVD outcome, death, or end of follow up (i.e. 2014). Time to event was calculated in years = time of CVD event (admission date) minus start of follow-up for those who had and CVD event, and end of follow-up

minus start of follow-up for those who did not have CVD event. The hospital discharge diagnoses (main and secondary) derived from the NPR were same as used for study I.

3.5 COVARIATES

The following variables were selected as covariates: age, gender, socioeconomic position (SEP), hypertension, and diabetes, all assessed at baseline (W1). The reason to consider these as confounders was that they have been previously associated with depression and CVD independently and do not come in the causal pathway (when considered at baseline) between depression and CVD (133, 184, 185). History of ischemic heart disease and stroke were measured at W1 and were considered as previous history of CVD and persons reporting this were excluded from analysis as mentioned earlier. We considered smoking, hazardous alcohol use, BMI and physical inactivity as potential mediators since they are established risk factors for both depression and CVD but are also likely to come in the causal pathway (9, 186-190). For study III only age and BMI were considered as covariates. Covariates were recorded from W1 in general, for smoking and physical activity, data was only available in W2.

Gender and *Age at W1:* Age was categorized into 20-30 years, 31-40 years, 41-52 years and >52 years. Age 20-30 years was considered as reference.

Socioeconomic position (SEP) in W1 was measured through occupational groups defined according to the Nordic Standard Occupational Classification (NSOC) of 1989 (191). SEP was classified into five groups: high/intermediate level salaried employees; assistant non-manual employees; skilled workers; unskilled workers; and self-employed (including farmers). High/intermediate level salaried employees was the reference as this group is relatively less disadvantaged than the other groups.

Physical inactivity was defined as not exercising regularly (i.e. at least three times a week).

Smoking habits reported in W2 was classified as regular smoker, occasional smoker, previous smoker and never smoker (192). Never smoker was used as reference category as they are expected to have the lowest risk of CVD.

Hazardous alcohol use in W1 and W2 was assessed by the Alcohol Use Disorders Identification Test (AUDIT) tool (193) and dichotomized according to the Swedish cut-off points (≥8 points for men and ≥6 points for women) (194).

Treatment for psychiatric disorders was assessed using questions inquiring whether the participant had sought psychiatric consultation in either W1 or W2.

Diabetes mellitus and *hypertension* at W1 were assessed by asking the participants if they suffered, at present or in the past, from diabetes or hypertension.

Body mass index (BMI) was calculated from height and weight (i.e. weight in kg divided by height in m^2).

For variables for which data was available from both W1 and W2, a combined variable was created for both waves indicating presence in both waves or maximum value in either wave for a continuous variable (e.g. body mass index).

3.6 STATISTICAL METHODS

3.6.1 Descriptive statistics

Mean and standard deviation were used for quantitative variables, and frequency and percentage for categorical variables for all four papers. Also, for the specific studies in this thesis, those who had history of myocardial infarction or stroke (baseline CVD); 2.6 %(n=267) were excluded, so there is a CVD free population to follow. This information was collected based on self-report at baseline.

3.6.2 Missing data

All participants with partially missing responses were approached through telephone calls to fill this data. Imputation of missing values for MDI was accomplished when there were missing answers for one or two of the ten questions. If answers were missing for more than two questions, the response was left as missing. The missing answers were imputed with the mean value of the questions in the answered items. The number of missing answers for three or more questions was low, 0.2% (n=23) in W1 and 1.4% (n=121) in W2. The maximum number of missing values for questions on personality trait neuroticism (paper II) were as follows; somatic trait anxiety 0.3% (n=29), stress susceptibility 0.3% (n=29) and for embitterment 0.4 % (n=29). As there was no partially missing data on the SSP, no imputation was done for the three subscales i.e. somatic trait anxiety, stress susceptibility and embitterment. SEP had missing data of 24%, due to administrative reasons. Additional information on

occupation was derived from reported main daily activity and included in the above categories if the participants reported to be retired, students or self-employed. This reduced the missing in SEP to 5 %. Missing in smoking was 17 % consisting of 1719 (16%) who did not participate in in W2 and 146 (1.4%) did not respond to questions related to smoking. Missing in physical inactivity was 17 % consisting of 1719 (16%) who did not participate in W2, and 112 (1.0%) did not respond to questions related to physical inactivity.

3.6.3 Logistic and Cox regression analysis for paper I

For paper I logistic regression was used as participants were followed for CVD outcome through self-reports in W3 and in 2008 to 2011 through NPR. The reason to include both self-reports and register data was to reduce the chance of self-reporting bias. However, after additional register linkage we received corresponding register data for 2001-2014.Cox regression was employed to estimate hazard ratios (HR) and corresponding 95% confidence intervals (95% CI) were calculated. To assess severity of depression, those depressed were categorized into mild, moderate and severe. For the sub-analyses including depression and anxious distress; we used those with neither depression nor anxious distress as reference. Separate models were constructed to adjust for confounders and potential mediators. Subgroup analysis for IHD and stroke were also done. Model 1 was adjusted for socio demographic factors including age, gender and SEP, and model 2 was additionally adjusted for diabetes, hypertension, and lifestyle factors (i.e., smoking, physical inactivity, hazardous alcohol use and BMI)

3.6.4 Cox regression analysis for paper II

Cox regression models were constructed to determine hazard ratios with 95 % confidence intervals using survival analysis. Adjustments in models were the same as for paper 1.

Interaction analysis

Additive interaction was estimated measuring interaction on an additive scale as it is more appropriate for assessing the public health importance (195) and based on dummy variables of depression and levels of neuroticism. Four dummy variables were created; low level neuroticism with no depression (reference), low level neuroticism with depression, high level neuroticism with no depression, and high-level neuroticism with depression. Synergy index (S) was calculated to confirm if

additive interaction was present. S = 1 means no interaction or exactly additively; S>1means positive interaction or more than additivity; S<1means negative interaction or less than additivity. S can range from 0 to infinity.(196)

Further, multiplicative interaction was estimated using main effect model with and without multiplicative interaction between depression and neuroticism and p-value was calculated using the Log likelihood test. Multiplicative interaction is often checked to see the magnitude of the interaction effect.

3.6.5 Logistic regression for paper III

Comparative analysis between depressed and non-depressed participants was done where appropriate using Student t-test and chi square test. We could not do cox regression for paper III due to smaller sample size. Logistic regression was used to calculate odds ratios (OR) and corresponding 95% confidence intervals (95 %CI) for depression and CVD according to COMT Val^{158}Met, adjusting for age and body mass index (BMI). We did not adjust for additional covariates as we thought that it will not have effect on the genetic makeup .To determine the combined effect of COMT Val^{158}Met and depression on future risk for CVD, logistic regression analyses were performed using the four dummy variables; Met carriers (A/A plus A/G) with no depression (reference), Met carriers (A/A plus A/G) with depression, Val/Val (G/G) with no depression, and Val/Val (G/G) with depression. Additive and multiplicative interaction was estimated in the same way as for paper II

3.6.6 Cox regression analysis for paper IV

Cox regression models were constructed to determine hazard ratios with 95 % confidence intervals using survival analysis. Exposure was depression and non-cardiovascular morbidity. Four dummy variables were created; no non-cardiovascular comorbidity with no depression (reference category), non-cardiovascular comorbidity with depression, non-cardiovascular comorbidity with no depression, and non-cardiovascular comorbidity with depression. Adjustments in models were done as for paper II Additive interaction was calculated with synergy index as for paper II

4 RESULTS

4.1 SEVERITY LEVEL OF DEPRESSION (AND ANXIOUS DISTRESS) AND CVD (PAPER I)

For descriptive statistics of all variables, see table 3. Distribution of covariates among PART participants overall and stratified by depression status. The prevalence of depression, according to MDI was 14.4% (n=1488); 5.2% (n=534) had mild, 3.5% (n=367) moderate and 5.6% (n=587) had severe depression. Applying the DSM-IV algorithm, the overall prevalence of depression was 7.6% (n=790). Anxious distress was present in 23 % (n=2522) of the participants. At follow-up 6.5% (n=676) had CVD (Table 4).

Table 3. Distribution of covariates among PART participants overall and stratified by depression status.

	Overall	**Depressed[1]**	**Not depressed**	**P-value[2]**
	N=10341	n=1488	n=8832	
	N (%)	n (%)	n (%)	
Mean age (SD) in years	41.3 (12.4)	39.56 (11.9)	41.67 (12.5)	<0.001
Age group (in years)				
19-30	2595 (25.1)	432(29.0)	2160(24.5)	<0.001
31-40	2476 (23.9)	364(24.5)	2102(23.8)	
41-52	2733(26.4)	421(28.3)	2308(26.1)	
>52	2534(24.5)	271(18.2)	2259(25.6)	
Male gender	4620 (44.0)	463 (31.1)	4146 (46.9)	<0.001
Socio-economic position				0.38
High and intermediate level salary	4702 (45.5)	493 (37)	4206 (50.2)	
Assistant –non-manual workers	1438 (13.9)	222 (16.7)	1215 (14.5)	
Skilled workers	665 (6.4)	94 (7.1)	570 (6.8)	
Unskilled and semiskilled workers	1204 (11.6)	233 (17.5)	968 (11.6)	
Self-employed (other than professional)	729 (7.0)	80 (6.0)	649 (7.7)	
Retired	435(4.2)	122(9.2	311(3.7)	
Students	552(5.3)	88(6.6)	459(5.5)	
IHD	193 (1.9)	47 (3.2)	143 (1.6)	<0.001
Stroke	86 (0.8)	23 (1.5)	63 (0.7)	0.003
Hypertension	716 (6.9)	126 (8.5)	590 (6.7)	0.01
Diabetes mellitus	221 (2.1)	38 (2.6)	181 (2.0)	0.20

Table 3 continued

Smoking				<0.001
Regular	1289 (12.4)	306 (24.5)	983 (13.6)	
Occasional smoker	889 (8.6)	148 (11.9)	741 (10.3)	
Ex-smoker	2502 (24.1)	331 (26.5)	2171 (30.0)	
Never smoker	3796 (36.6)	462 (37.0)	3333 (46.1)	
Physical inactivity	3936 (46.3)	697(55.9)	3237(44.6)	<0.001
Mean BMI (SD) in kg/m^2	24.97 (3.9)	25.13 (4.4)	24.93 (3.7)	0.1
Hazardous alcohol use	2605 (25.2)	544 (36.6)	2060 (23.3)	<0.001
Sought treatment for psychiatric disorders	2365 (22.8)	821 (55.2)	1542 (17.5)	<0.001
Severity of depression (MDI)[1]				
Mild		534 (5.1)		
Moderate		367 (3.5)		
Severe		587 (5.6)		
Anxious distress symptoms				<0.001
Mild	1729 (16.7)	539 (36.3)	1189 (13.5)	
Moderate/severe	793 (7.7)	628 (42.3)	165 (1.9)	
Personality trait neuroticism				
Lowest	2828(27.34)	40(3.2)	2788(38.5)	
Middle	2798(27.05)	198(15.9)	2600(35.9)	
highest	2866(27.7)	1004(80.8)	1862(25.7)	<0.001
Non cardiovascular morbidity	1356 (13.1)	323(21.7)	1026 (11.6)	<0.001

[1] Depression assessed by Major Depression Inventory, [2]Pearson chi square test and independent sample t test were used as appropriate

Table 4. Distribution of CVD in PART participants overall, and stratified by depression status (paper I, II and IV).

	Overall	**Depressed[1]**	**Not depressed**	**P-value[1]**
	N=10341	n=1488	n=8832	
	n (%)	n (%)	n (%)	
Cardiovascular diseases	676 (6.5)	109 (7.3)	564 (6.4)	0.09
Ischemic/hypertensive heart [2]	435 (4.2)	71(4.8)	361(4.1)	0.12
Stroke [3]	298 (2.9)	53 (3.6)	245 (2.8)	0.05

[1] Chi square test was used to determine p values, [2] (ICD10 codes: I11–13, I20–25, 10: I50), I73–74), [3] (ICD10: I60–67 and I69)

Depression was associated with risk of future CVD (OR 95% CI 1.9 (1.4, 2.5). The association weakened after adjusting for confounding factors (age, gender) into account OR 95% CI 1.7 (1.2, 2.3), but remained increased in the final model after adjusting for SEP, diabetes, hypertension and lifestyle factors (OR 95% CI 1.5 (1.1, 2.1). Detailed results on severity level of depression and CVD are reported in the paper. Repeating the analyses using Cox regression (not presented in paper I) showed that depression was associated with increased risk for CVD (HR 95% CI 1.5 (1.1, 2.0), the risk remained after adjustment for confounders and mediators in the final model (HR 95% CI 1.3 (1.0, 2.0). Regarding severity of depression, overall increased hazard ratios of 1.3 to 2.0 were seen for the different severity levels of depression, with the highest HR for moderate depression (HR 95 % CI 2.0 (1.3, 3.2). Additionally, those who were depressed with concomitant anxious distress were at higher risk for CVD; HR 95% CI 2.0 (1.2, 2.3) (Figure III. Adjusted Hazard ratio for CVD according to severity level of depression, Table 5.)

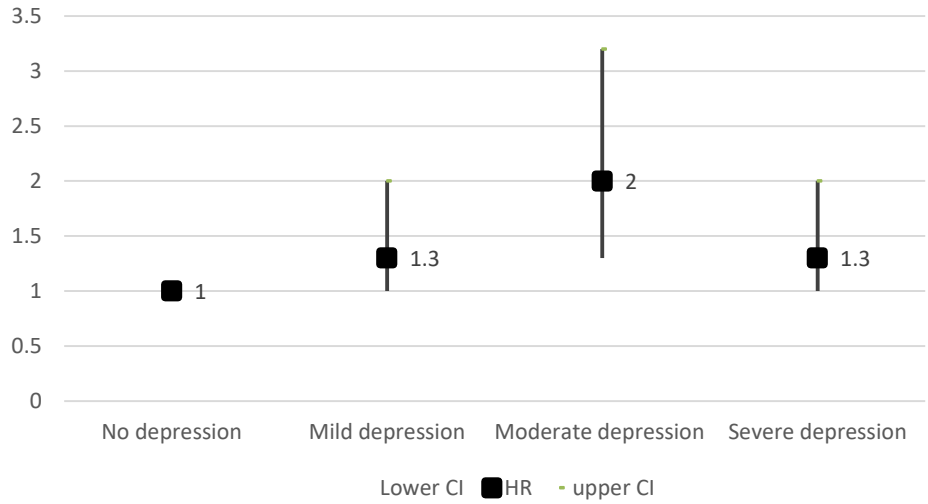


Figure III. Adjusted hazard ratio[1] for CVD according to severity level of depression

[1]Adjusted for age, gender SEP

4.2 DEPRESSION, HIGH LEVEL NEUROTICISM, AND CVD (PAPER II)

Mean (SD) t-score for neuroticism was 145 (SD 24.0); somatic trait anxiety 47.9 (SD 9.7), stress susceptibility 51.1 (SD 8.1) and for embitterment 46.5 (SD 9.9) respectively. High level of neuroticism was present in 27.7% (n=2866) of the participants and of these persons 65.0% (n=1862) were not depressed and 35.0% (n=1004) were depressed. Table 3. At follow-up 6.5% (n=676) had CVD.

Having high level of neuroticism was associated with increased risk of CVD; HR=1.5 (95% CI 1.2, 2.0). Those who were depressed and had high level of neuroticism had a further increased risk for CVD (HR 95% CI 2.0 (1.3, 2.6)) versus those who were depressed and had low level of neuroticism (HR 95% CI 1.0 (0.4, 2.1)) (Figure IV. Adjusted Hazard ratio for CVD according to depression status and level of neuroticism, Table 5. Depression severity, neuroticism, Non-cardiovascular morbidity and risk of CVD in depressed participants) Additive interaction, revealed a synergy index of 1.7(95% CI 0.4, 6.3). However, no evidence for multiplicative interaction between depression and neuroticism for risk of CVD was seen (p-value for log likelihood ratio= 0.4).

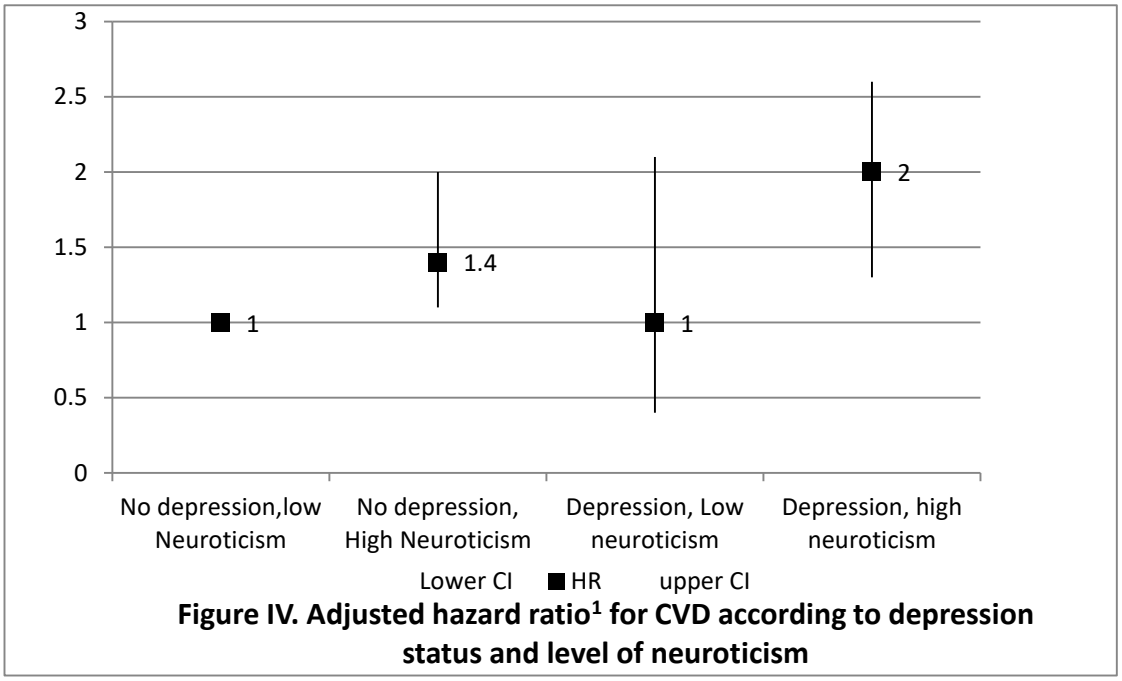


Figure IV. Adjusted hazard ratio[1] for CVD according to depression status and level of neuroticism

[1]Adjusted for age, gender SEP

Table 5. Depression severity, neuroticism, non-cardiovascular morbidity and risk of CVD[1] in depressed participants

	CVD n=537 Model 1[2] HR 95 % CI	Model 2[3] HR 95 % CI
Depression		
No	Ref	Ref
Yes	1.5 (1.1,2.0)	1.3 (1.0,2.0)
Level of depression (MDI)		
No depression	Ref	Ref
Mild depression	1.3 (1.0,2.0)	1.2 (1.0,2.0)
Moderate depression	2.0 (1.3,3.2)	2.0 (1.2,3.1)
Severe depression	1.3 (1.0,2.0)	1.1 (1.0,2.0)
Depression (MDI) with/without symptoms of anxious distress		
No depression or anxious distress	Ref	Ref
Anxious distress	1.03 (1.0,1.4)	1.0 (1.0,1.4)
Depression alone	1.3 (1.0,2.5)	1.3 (1.0,2.4)
Depression with anxious distress	2.0 (1.1,2.3)	1.4 (1.0,2.0)
Depression and Neuroticism		
No depression & low neuroticism	Ref	Ref
Depression & low neuroticism	1.0 (0.4,2.1)	1.0 (0.4, 2.3)
No depression & high neuroticism	1.4 (1.1,2.0)	1.4 (1.1,2.0)
Depression & high neuroticism	2.0 (1.3,2.6)	2.0 (1.2,2.4)
Depression and non-cardiovascular morbidity		
No depression & No Non-cardiovascular morbidity	Ref	Ref
Depression & No Non-cardiovascular morbidity	1.4 (1.0,2.0)	1.3 (1.0,2.0)
No depression & Non-cardiovascular morbidity	1.5 (1.1,2.0)	1.4 (1.0,2.0)
Depression & Non-cardiovascular morbidity	2.1 (1.4,3.4)	2.0 (1.1,3.3)

[1] Baseline CVD excluded, [2] Adjusted for age, gender, SEP, [3] Adjusted for age, gender, SEP, baseline DM, baseline hypertension, physical inactivity, BMI, smoking and hazardous alcohol consumption.

4.3 DEPRESSION, HIGH ACTIVITY COMT VAL ^{158}MET, AND CVD (PAPER III)

Out of the 3525 participants with COMT Val^{158}Met data 1094 (31.0%) had Met/Met genotype, 1720 (48.0%) were Met/Val and 711 (20.2%) were Val/Val. The genotype distribution was in Hardy Weinberg equilibrium (p=0.31). Those homozygous for Val/Val showed a borderline reduced risk for depression (OR 95% CI 0.70 (0.60, 1.0). Similar risk estimates were seen after stratification for gender. However, those who had Val/Val had an increased risk for future CVD (OR95% CI 1.3 (1.0, 1.7)). Stratification for gender showed that the OR point estimate for risk for later CVD was higher among women than men (OR 95% CI 1.5 (1.0, 2.4) versus (OR 95% CI 1.1 (1.0, 1.7)).

Those with depression and the high COMT enzyme activity genotype (Val/Val) had a three times higher risk of later CVD (OR 95% CI 3.6 (2.0, 6.6)) compared to those non-depressed carrying the Val/Val allele. This effect on risk for CVD was higher in women compared to men (OR 7.0 (95% CI, 3.0, and 14.0) versus OR (95% CI 2.1, (1.0, 6.8)). (Figure VI. Adjusted *Odds ratio for CVD according to depression status and COMT Val [158] Met, Table 6.)

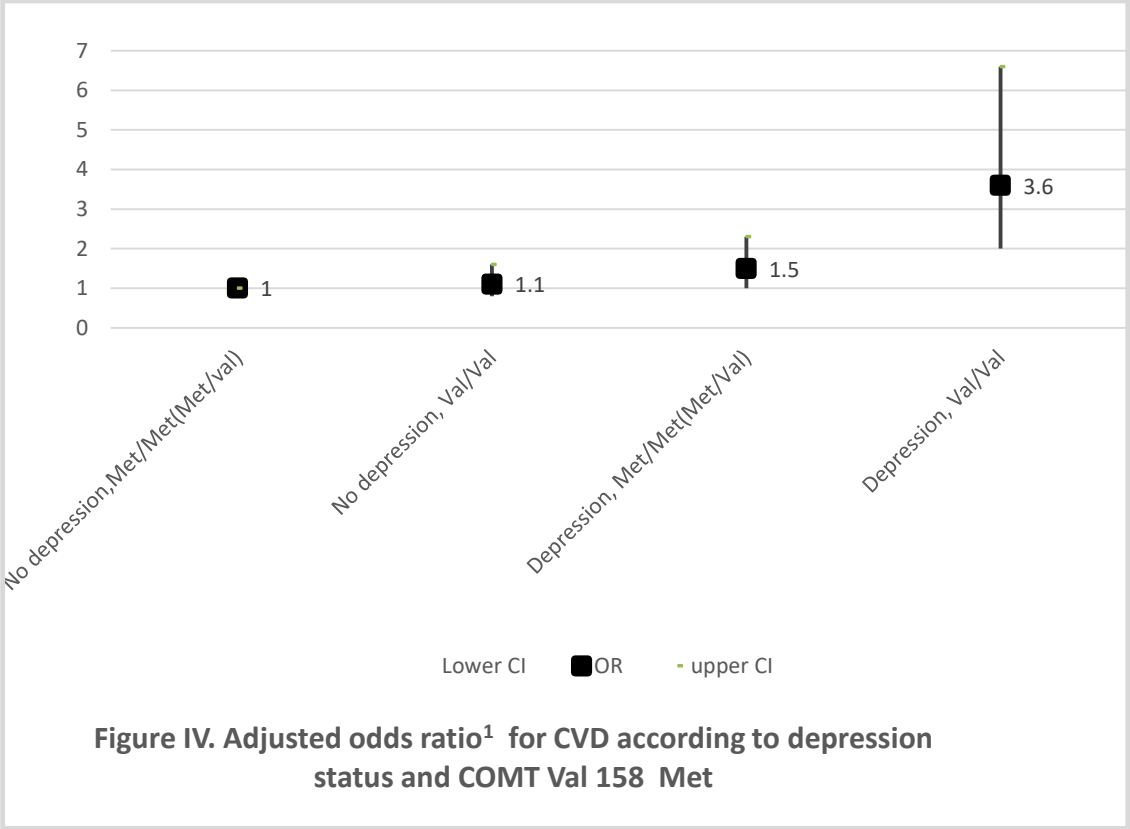


Figure IV. Adjusted odds ratio[1] for CVD according to depression status and COMT Val 158 Met

[1]Adjusted for age and BMI

Table 6. Interaction between COMT Val[158]Met and depression for future risk of CVD, stratified by gender.

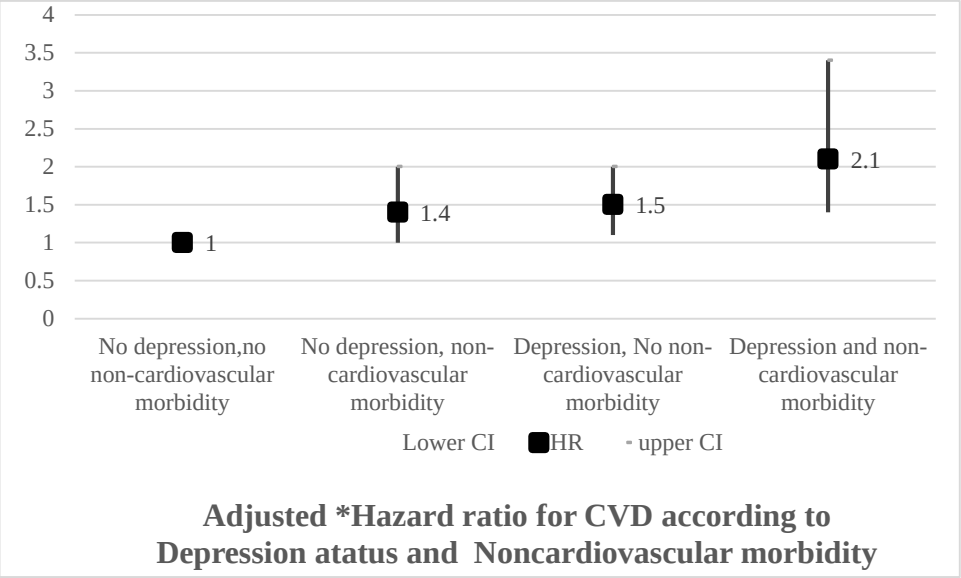
	All n=3525		**Men** n=1495		**Women** n=2030	
	Met/Met or Met/Val	Val/Val	Met/Met or Met/Val	Val/Val	Met/Met or Met/Val	Val/Val**
	n=2814	n=711	n=1179	n=316	n=1635	n=395
Depression			**n CVD/n Non-CVD**			
No	146 /2205	42/576	102/947	31/258	44/1258	11/318
Yes	33/430	15/78	15/115	4/23	18/315	11/55
			Odds ratio (95% confidence interval)[1]			
Depression						
No	1 (Ref)	1.1(0.8,1.6)	1 (Ref)	1.1(0.73,1.7)	1 (Ref)	1.0(0.50,2.0)
P values	-	0.5	-	0.5	-	0.10
Yes	1.5(1.0,2.3)	3.6(2.0,6.6)	1.8(1.0,3.4)	2.1(1.0,6.8)	2.0(1.1,3.5)	7.0(3.0,14.0)
P values	0.03	<0.001	0.05	0.20	0.01	<0.001

[1] Odds ratio (OR) for Val/Val (G/G) with no depression, Val/Val (G/G) with depression and Met carriers (A/A plus A/G) with depression, adjusted for age and body mass index. Met carriers (A/A plus A/G) with no depression was the reference group.

4.3.1 DEPRESSION, NON-CARDIOVASCULAR COMORBIDITY AND CVD (PAPER IV)

Non-cardiovascular morbidity was present in 13.1% (n=1356) of the participants. (Table 3. Distribution of covariates among PART participants overall and stratified by depression status.)

Non-cardiovascular morbidity was associated with an increased risk for CVD (HR 95% CI 2.0 (1.8,2.6).Those who were depressed and had non-cardiovascular morbidity, were at increased risk of CVD; HR 95% CI 2.1 (1.3, 3.4) in analyses adjusted for age, gender and SEP versus those who were depressed and did not have non-cardiovascular comorbidity (HR 95% CI 1.5 (1.1, 2.0)). The association remained after adjusting for diabetes, hypertension, physical activity, smoking, BMI and hazardous alcohol use. (Figure V. Adjusted Hazard ratio for CVD according to depression status and non-cardiovascular morbidity, Table 5)



[1]Adjusted for age and BMI

5 DISCUSSION

5.1 MAIN FINDINGS

This thesis aimed to increase knowledge on the association between depression and CVD. The main findings of the thesis are that depression severity (especially with concomitant anxious distress) increased the risk for CVD, compared to those who were not depressed. Having depression and high level of neuroticism increases the risk of CVD compared to those depressed and with low level neuroticism. Those who have depression and have high activity COMT Val^{158}Met genotype are at increased risk of CVD compared to those depressed with low activity Val^{158}Met genotype. We also found that those depressed with non-cardiovascular morbid conditions were at increased risk of CVD compared to those depressed with no non-cardiovascular morbidity.

5.2 SEVERITY LEVEL OF DEPRESSION AND CVD

Severity level of depression increased the risk of CVD, although the results do not demonstrate a classic dose response effect. Moderately depressed persons showed increased risk for CVD compared to mildly and severely depressed. Further, those who were depressed and had anxious distress were at higher risk of CVD compared to those depressed without anxious distress.

Previous meta-analyses report about depression as a risk factor for CVD, however few studies to date have specifically studied the effect of different levels of severity of depression (10, 137). In the Nova Scotia Health Survey in 1995 (n=1302) depression was assessed as a quantitative score using the centre for epidemiological studies–depression scale. The study reports an independent and dose response effect between depression and incident coronary heart disease (152). The results of this study are limited by the fact that it was either a small population based sample or only those whose records were available in administrative healthcare database were included. In analyses of 4538 clinical participants, Abramson et al used the same scale and found an increased risk for heart failure for those who scored > 16 on the scale((low (0-7), medium (8-15), and high (≥16)) (197). The results of this study is limited by the fact that it included only elderly hypertensive people. In 2015, Seldenrijk et al from the Netherlands study of depression and anxiety (n=2510) concluded that people with current depression have a 2- to 3-fold increased risk of CVD at follow-up of 6 years, and

additionally they demonstrated a dose-response association for severity level of depression, i.e. the higher the number of symptoms the higher the subsequent CVD risk (153). Our study is in line with the above findings, however we did not demonstrate a dose response relation between level of severity of depression and CVD. The reason for this could be that Seldenrijk used the inventory of depressive symptomatology, used only in outpatient settings while we used the major depression inventory used in general population for assessment of depression. Additionally, our study included a large healthier population-based sample in which CVD outcomes were followed through both register and self-reports, while the study by Seldenrijk et al included a clinical, less healthy sample with self-reported CVD outcomes. It is for this reason that the prevalence of depressed in the PART was 14 %, while in the study by Seldenrijk et al the prevalence of depression or anxiety was 78 %. The lack of dose response association in our study could presumably be also explained by those who had severe psychiatric symptoms participated less in this study. This might have resulted also in underestimation of the risk (171). Also people with severe depression seek treatment for psychiatric disorders more commonly than those with milder forms and hence are more likely to be treated (198).

Studies have been reported on the association of anxiety and CVD. In a 37-year follow-up study including 49,321 men from Sweden, anxiety disorders were strongly associated with incident CHD and acute myocardial infarction (MI) (199). The results of this study is limited by the fact that there was no intermediate follow-up and anxiety disorders rather than anxious distress was assessed in this study. Another 7-year follow-up cohort study of 25,895 Finnish men and women reported significant associations of anxiety with elevated risk of CHD (200). The DSM-5 anxious distress is longitudinally predictive of a worse clinical course, it supersedes comorbid DSM-IV-based anxiety disorder diagnoses as a longitudinal predictor (201). Our findings that depression with anxious distress increases risk of CVD is unique and is predictive of long-term public health and clinical impact on care of depressed persons who are at risk of CVD.

5.3 DEPRESSION, HIGH LEVEL NEUROTICISM AND CVD

We found that co-existence of depression with high levels of neuroticism increased the risk of CVD compared to depressed with low level of neuroticism. Some studies have previously shown associations between depression, neuroticism and CVD.

Marijnissen et al concluded from a 9-year follow-up study of 2050 participants, Longitudinal Aging Study Amsterdam (LASA), that older persons with depression and low levels of neuroticism had a higher risk of developing stroke, thus indicating a negative interaction in predicting future risk of CVD (202). These results are in contrast with our study that suggests a positive interaction between neuroticism and depression in predicting CVD. The reasons for this contrast could be that outcome assessment for CVD was based on self-reports and medication-based diagnoses. This might have resulted in misclassification of outcome thus effecting the risk estimates. Secondly LASA had relatively reduced power due to selective dropout of persons with missing data. Also, the age group in LASA was older than the PART study. A recent study from Sweden (n= 323) reported that depression and neuroticism might be contributing to decreased smoking cessation behaviour, thus increasing the risk of CVD (203). This lack of smoking cessation behaviour in persons with depression and high level of neuroticism could contribute to risk of CVD. However, more studies are required to confirm this hypothesis. Our findings that those who are depressed and have high levels of neuroticism are at increased risk of CVD, is of importance for the clinical management of this group.

5.4 DEPRESSION, HIGH ACTIVITY COMT VAL ^{158}MET AND CVD

We found that persons with depression and high activity COMT Val ^{158}Met genotype have an increased risk of CVD. The risk was higher in women compared to men.

A previous meta-analysis did not show any association between COMT Val ^{158}Met and depression, however the results were limited by substantial heterogeneity (204). Previous studies focussing on the combined effect of depression and COMT Val ^{158}Met for risk of CVD are non-existent. Most studies talk about the association of COMT Val ^{158}Met with CVD, however whether high or low activity COMT Val ^{158}Met is associated with CVD, is still under debate. A case-control study was conducted on 305 young ischemic stroke subjects aged $\leq$50 years from Taiwan concluding that COMT Val ^{158}Met polymorphism was significantly associated with ischemic stroke among females (205). Hagen et al reported from the Nord-Trøndelag Health Study (HUNT) (n=2979) that individuals with high activity Val/Val genotype had a lower mortality rate due to heart diseases.(206) Although later on from the same study, they reported that high COMT activity (Val/Val genotype) was overrepresented in Norwegians with systolic hypertension (≥140 mm Hg) (n=2591)

(207). Voutilainen et al in the population-based prospective cohort of 792 men, the Kuopio Ischemic Heart Disease Risk Factor Study, suggested that low activity COMT Val ^{158}Met was associated with a higher risk of acute coronary events (208). Similar results have been demonstrated in a Japanese study on 735 men (209). We found that those who were depressed and had high activity COMT Val ^{158}Met genotype were associated with increased risk of CVD. These findings were confirmed by Eriksson et al who reported a protective effect of low activity COMT Val ^{158}Met against myocardial infarction in a Swedish and Finnish hypertensive sample (n=522) (161). However, these results are limited by the fact that this study did not focus on depression. Compared to the HUNT study which included nondiabetics and outcome included IHD related mortality, our study included all participants' outcomes being myocardial infraction or stroke. Hence our study did not have any selection bias based on disease or gender.

Our finding of high activity COMT Val ^{158}Met associated with increased risk for CVD in women compared to men might be due to following reasons. The gender-based difference might be explained by the difference in oestrogen activity between men and women and COMT is key in oestrogen metabolism. Thus, the association between COMT Val ^{158}Met and CVD in females might reflect altered levels of oestrogen and its metabolites in men and women (205).

5.5 DEPRESSION, NON-CARDIOVASCULAR MORBIDITY AND CVD

We found that the coexistence of depression and non-cardiovascular morbid conditions increased the risk of CVD compared to depressed with no non-cardiovascular morbid condition. The effect remained after adjusting for adverse lifestyle factors.

Some studies have reported associations between depression and morbidity.(59, 210) We found only one study focusing on co-existence of depression and morbidity on CVD. The study included 6,394 subjects who participated in the First National Health and Nutrition Examination Survey (NHANES I) conducted between 1971 and 1975 and later followed-up between 1982 and 1984 (169). Depression and prevalent chronic medical conditions was assessed at baseline and participants were followed up for CVD mortality and incident medical conditions. The study reported that having more severe depressive symptom increased the risk of CVD mortality at follow-up (HR 95%CI 1.5 (1.2, 1.8)), however when

considering demographics, lifestyle behaviors, prevalent and incident chronic medical conditions, the risk estimates weakened (HR 95% CI 1.1 (0.9, 1.4)). The study therefore concluded that the association between depression and CVD mortality was partially mediated by prevalent/incident comorbidity. Our study shows that depression with coexisting morbidity increases the risk of CVD compared to non-depressed or those without non-cardiovascular morbidity. The study by Atlantis et al is different from our study with respect to study designs, assessment of depression, type of comorbid conditions and CVD outcome. Also, we considered non-cardiovascular morbidity as an effect modifier while the former study adjusted the results for it. This might have led to underestimation of the risks in the former study as adjusting for comorbid might have accounted for most of the association between depression and CVD. Also, the former study included the conventional risk factors (diabetes, hypertension) in the definition of comorbidity, whereas we considered only non-cardiovascular and used incidence of CVD rather than CVD mortality.

Several reasons may contribute to the relation between depression, non-cardiovascular morbidity and CVD. Firstly poor medication adherence occurs in depressed patients which becomes more serious when it is linked to noncompliance to medications for a chronic condition (211). Secondly, many patients with morbidity do not undergo systematic depression screening in routine practice due to time constraints and therefore missing diagnosis of depression in a clinic visit might have underestimated the risk (212). Thirdly, the studies are still scarce on the temporality of depression and non-cardiovascular morbidity. Depression might lead to more chronic physical conditions and it might happen in the reverse direction also (213). Also it is still a point of debate whether to treat depression first or the chronic illness first, which might result in people with depression untreated.

5.6 POTENTIAL UNDERLYING MECHANISMS FOR THE FINDINGS IN THIS THESIS

Some mechanisms have been proposed discussing the relation between depression and CVD. The pathophysiological mechanisms behind depression include metabolic, immune-inflammatory, autonomic and hypothalamic pituitary axis dysregulation, all of which affect the incidence of CVD (214). Elevated depression symptoms are associated with augmented immune cell mobility via

leukocyte mobilization in patients suffering from heart failure (215). Depression and anxiety results in expedited progression of atherosclerosis and other cardiovascular conditions(216). These augmented immune cell mobility leading to expedited atherosclerotic process might be responsible for the link between severe levels of depression and CVD. However further studies are required to prove this concept.

The underlying mechanisms for anxiety has been hypothesized as increased cardiovascular reactivity to stress and resting heart rate, decreased heart rate variability, bar reflex dysfunction, and greater variability in ventricular repolarization (217). Additional mechanisms described in literature suggest that anxious depression is associated with distinct neurobiological findings in the hypothalamic pituitary axis (218), genetics (219) and chronic inflammatory phenomenon (220).

Previous studies elucidate underlying biological mechanisms between neuroticism, depression and CVD. Čukić and Bates recently published results from a nationally representative sample (n=1255) from United States showing that heart rate variability is a reliable biomarker for neuroticism (221). They suggested that higher neuroticism was associated with reduced heart rate variability equally under rest and stress. Reduced heart rate variability has been associated with elevated levels of CVD (222). Hence based on our results, we suggest that this reduced heart rate variability might be the underlying linking mechanism between neuroticism and depression, thus increasing the risk of CVD. Marijnissen et al reported a negative interaction between neuroticism and atherosclerosis (223). This means that people scoring high on neuroticism and having depression might less vascular risk factors while those scoring low on neuroticism might have more vascular risk factors as a potential explanation for the increased risk of future stroke (202, 224). In contrast our results suggest, that since both depression and neuroticism are independent risk factors for CVD, the vascular risk refactors might be shared and hence leads to increased CVD. However more studies are required to confirm our findings at biological level.

The function of COMT Val^{158}Met genotype has been under constant debate. One common concept is of warrior/worrier model by Goldman which talks about balance in stress resiliency (Val158 allele) versus cognitive function (Met158 allele) (225). The underlying mechanism between COMT Val^{158}Met genotype, depression and CVD could be following. Firstly, persons with the at risk allele Val/Val has been

reported to have higher heart rate, and increased startle potentiation to aversive stimuli relative to the Val/Met or Met/ Met allele (226). This is of course linked to catecholamines which have well-known effects on the cardiovascular system, e.g. blood pressure regulation (227, 228). This along with depression with anxious distress might affect the heart rate variability which is a linking mechanism between depression and CVD (229). Secondly, it has been reported that Val/Val women carriers have higher cortisol(230) levels compared to Met/Met Allele which might be linked to higher blood pressure levels and central obesity.

The underlying mechanisms shared between depression, non-cardiovascular morbidity leading to CVD is largely unknown. Inflammation indicated by circulating levels of interleukin-6, C-reactive protein, and fibrinogen may be an important biological mechanism (231). Inflammation is also an underlying shared mechanism between depression and CVD (232). In depressed people, additional comorbid condition might trigger a pathway of inflammation contributing to risk of CVD. Many of these pathways are driven by chronic oxidative stress and a reduction in anti-ageing molecules (233).

5.7 METHODOLOGICAL STRENGTHS AND LIMITATIONS

5.7.1 Design

The sub studies in this thesis all employed a cohort design. Cohort studies are similar to RCTs as they compare outcomes in groups except that the allocation of individuals to depressed or non-depressed groups is not random (and there is no intervention) (234). The study base was the adult population residing in the Stockholm County, all of whom had similar chance of being selected for the study. Additionally, large number of participants, and the assessment of exposure are also strengths. While we had a large population-based sample of 10341 people, however there was lack of power when we did interaction analysis. This is a limitation.

5.7.2 Selection bias

Subject selection bias: Factors affecting enrolment of subjects into a cohort study is less likely to introduce selection bias as it has to be related to both exposure and outcome. Outcome assessment in cohort studies has yet to take place (235). Participants in PART was a random sample of participants living in Stockholm County, both exposed and unexposed groups were at same likelihood to be selected

for the study, thus alleviating the chance of selection bias at the time of recruitment. The participation rates in W1 was 53 % is rather low, which is a limitation (171). The non-participation analysis revealed that male sex, being below 50 years of age, low income, low education, living alone and country of origin outside the Nordic countries were strong determinants of non-participation. Additionally, those who had history of inpatient psychiatric illness or suffered from severe psychiatric illness were less likely to participate.

In study III, only 41.7% provided DNA samples. Factors associated with public negation to consent to DNA bio banking in the PART have been reported. The participants thought that giving DNA was not relevant to them. They were uncomfortable about giving DNA information for research used for purposes other than the respective study were the reasons for low participation (173).

Loss to Follow up Bias: The follow-up in the PART study was over a 14-year period which was long and increases the chance of lost to follow-up bias. The follow-up rate of 61 % in W3 (n=5228) is low. This loss to follow-up might have resulted in underestimation of the risks. However, to address this lost to follow-up the outcome was assessed through the NPR in all four studies (for this thesis reanalysis of Study I was also done using the NPR instead of self-report outcome at W3). Hence the chance of lost to follow-up bias was very low and the reported risks for CVD therefore have good internal validity. Also, both the exposed and unexposed groups were at same likelihood of being followed up for outcome and hence this is also a strength of the study, limiting selection bias

Healthy participant effect: The PART study, since it is based on a population-based sample could have a healthy worker effect at the time of selection, as those who participated might be the ones who are healthier and were more likely to be employed. For example, the ones who had severe psychiatric illness (less healthy) were less likely to participate (171). This might have resulted in some degree of underestimation of the depression severity.

5.7.3 Information bias

Assessment of exposure: The strength is that the exposure of depression was assessed using MDI which is a validated, objective scale for assessment of depression(176). The MDI was self-administered by the participants, hence it was free from any interviewer bias. However, there might be some degree of

misclassification due to self-reporting (recall bias) by the participants, however non-differential of the outcome. This might have underestimated the risk.

In study , for the research question of severity of depression and risk of CVD, severity level of depression was assessed by using objective cut-offs of MDI into mild, moderate and severe (49). Additionally we used anxious distress, which is a specifier for severity of depression according to DSM-5(236). Including anxious distress as a severity measure for depression and following participants for risk of CVD is rather unique and has not been reported before to the best of our knowledge. However, one limitation of this study is that we did not have measurements on other specifiers of depression like melancholic features, with atypical features and with psychotic features.(236) Since PART was a long follow-up, our results are also limited by the fact that the status of depression, severity level of depression, level of neuroticism could have changed for participants, thus leading to some degree of misclassification of non-differential type, thus underestimating the risks.

In study II, neuroticism was assessed using the Swedish scale of personality which is a validated tool for Swedish population(180). Since this is a validated scale for assessment of neuroticism, the chance of misclassification of exposure was minimal. However, since the follow-up in PART study is long, there might have been changes in the level of neuroticism overtime , and this might have resulted in misclassification of exposure , thus leading to changes in risk estimates.

We used candidate gene approach for the genetic study (study III), which although is now overwhelmed by the rapidly rising genome wide studies, but the chances of false positive associations are relatively less in candidate gene approach studies (237). Hence this approach minimises the chance of misclassification of exposure.

The method of assessment of morbidity (study IV), might have resulted is misclassification of exposure due to self-reporting bias (recall) by the participants. However, this misclassification of exposure is non-differential, i.e. the chance of self-reporting bias was same in both depressed and non-depressed groups, thus leading to underestimation of the risk. Another issue in study IV is that we cannot comment on temporality of the relation between depression and non-cardiovascular morbidity as both were assessed at the same time. However, as the main outcome of importance was the CVD outcome, assessing temporality between depression and non-cardiovascular morbidity was of less importance. We also cannot determine

whether the recall period for the morbidity assessment was short or long and this is a limitation of the study, as the longer the period of recall , the more the chance of recall bias(238). However a more objective way of assessing comorbidity using scales or diagnostic tests for the large number of comorbid conditions would have been cost defective. Another way of measuring morbidity is Charlson comorbidity index(239). However we could not use it as it includes morbidity like myocardial infraction and stroke, which are not part of non-cardiovascular morbidity.

Assessment of outcome: The CVD outcome was assessed using the NPR in all 4 studies which is a reliable measure (125, 240). This alleviates the chance of misclassification of outcome. Since the CVD outcomes were taken from NPR, the diagnosis of CVD was based on objective clinical diagnostic criteria by the physicians/cardiologist. The NPR has excellent coverage hence loss of follow-up at outcome assessment was minimal. Also, participants with history of baseline CVD were excluded from the analysis to avoid reverse causality and misclassification of outcome.

5.7.4 External Validity and statistical power

The low participation rate reduced the sample size, resulting in a lack of statistical power in studies II, III and IV as there were low numbers of depressed individuals when stratifying on level of neuroticism, COMT Val ^{158} Met and non-cardiovascular morbidity. There was also limited external validity of the study as it cannot then be generalized to entire population or to those who had severe psychiatric illness (171, 172).

Confounders and mediators

Another strength of the study was that we were able to adjust the analyses for socio-demographics and CVD risk related lifestyle factors. Our results are limited by the fact that we could not adjust for dyslipidaemia which is also an important CVD risk factor. This inability of including dyslipidaemia might have overestimated the association.

There were limitations in assessment of SEP, as there was 24 % missing data in it. Such large missing data could falsely move the results towards or away from null. We then used an alternative method for SEP assessment using daily routine activity which reduced the missing information on SEP down to 6 %. There were limitations in the measurement of physical inactivity, since a validated physical activity tool was

not used, which could have resulted in falsely low or high physical inactivity levels. The measurement of alcohol intake was made through a validated tool AUDIT, which is a strength of the study resulting in correct measurement of alcohol intake. Smoking was assessed using the question of regular, occasional, previous and never smoker. While this information was optimal for our study but since we did not have information on the pack year history of cigarettes, we might have underestimated the effect of smoking on the association. Also, the physical activity status and smoking status was only recorded in W2, thus there was missing data for these covariates for those who did not participate in W2. This might have led to overestimation of the risk. The recording of information on diabetes and hypertension might have had some degree of recall bias as this information was based on questions thus leading to misclassification bias. We did not have data on psychotropic medications which are known to be linked to CVD (241), and hence the data could not be adjusted for them, which might have led to overestimation of the risk.

Interaction: Another strength of this thesis was that we tested interaction of depression with important concomitant factors like neuroticism, genetics (COM Val/Met) and comorbidity for risk of CVD. We used additive interaction mainly as it has large public health significance in study II, III and IV(195). Additionally, we also calculated synergy index which is a good tool to quantify the interaction between two variable and outcome (196). We also checked multiplicative interaction for study II and study III, but the effect was not significant, indicating that the magnitude of interaction might not be large.

6 IMPLICATIONS OF FINDINGS

6.1 PUBLIC HEALTH SIGNIFICANCE

Depression is a major public health problem and a large proportion of the affected persons go untreated(242). This thesis contributes to a further understanding of the etiology of cardiovascular disorders among depressed persons using unique population-based data. We found that severity level of depression increased risk of CVD, though not in a dose response pattern. The results imply that persons affected by depression need identification and control of CVD risk factors and simultaneous care and treatment for depression. Also, our study findings suggest that identification of at risk genotype like high activity COMT Val ^{158} Met might be useful to understand the risk of CVD for depressed persons. This also coincides with the rising trend of precision medicine which is expected to be the new era in treatment of patients according to their genetic susceptibility(243). The study on coexistence of non-cardiovascular morbidity and depression in increasing the risk of CVD is also of great importance in today's era when multi-morbidity is a rapidly rising syndrome impacting health, quality of life and health care resources. This interaction of depression with non- cardiovascular morbidity is of significant importance as it indicates that all patients with comorbidity need to be assessed for depression and treated accordingly. It is also important for the general public to understand that they might get depressed due to the coexisting morbid condition. Hence treatment for both the morbid condition and depression simultaneously should be started. As ignoring depression treatment might worsen the outcome of the morbid condition, thus leading to worse outcome of the morbidity and also increasing risk for CVD. These findings signal the government to implement strategies in primary care for earlier identification of both depression, CVD risk factors to prevent CVD

6.2 CLINICAL SIGNIFICANCE

The addition of knowledge on the coexistence of depression and neuroticism in developing CVD has more clinical implications for physicians and psychiatrist as people who are both depressed and have neuroticism are difficult to treat and might need earlier and more stringent care than the regular depressed population to reduce risk of CVD. This thesis contributes to science in further emphasizing and refining the relation of depression and CVD and contributes for consideration of depression as a conventional risk factor to CVD in addition to the existing ones.

6.3 FUTURE STUDIES

Future studies in this area can focus on replicating the genetic studies in other populations, using scales and more robust methods of identification of comorbid conditions in depressed patients and reconfirming the findings of increased risk for CVD. The genetic study of COMT Val ^{158}Met is novel for this population in terms of the association with cardiovascular diseases. Since this is the first study to report this association, more studies need to be replicated in other populations to improve external validity of this study. Intervention strategies to treat depression (antidepressants v cognitive behavioral therapy) and assessing CVD outcomes.

7 CONCLUSION

This thesis found an association between depression and CVD. We also found that severity level of depression and concomitant anxious distress increased the risk of CVD, compared to those not depressed. We also found that having depression and high levels of neuroticism increased the risk of CVD compared to depressed and low-level neuroticism. The existence of depression and high activity COMT Val ^{158}Met increased their risk of CVD compared to depress and those with low activity COMT Val ^{158}Met. Those who had depression and non-cardiovascular morbidity had an increased risk of CVD compared to non-depressed and those without non-cardiovascular morbidity.

Overall the thesis has contributed to better understanding to the relation between depression and CVD. It has also put light on some of the shared risk factors among depression and CVD and also how interaction of these risk factors with depression increase the risk of CVD. The thesis reconfirms the association of depression and CVD and strengthens the concept that more importance is needed for care and treatment of depression at mass level.

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9 APPENDICES

9.1 APPENDIX A. MAJOR DEPRESSION INVENTORY (MDI): SCORING KEY AND INSTRUCTION

Major Depression Inventory (MDI): Scoring Key

At the top, the diagnostic demarcation line is indicated and at the bottom, the total scores of the 10 items are summed up.

		How much of the time ...	All the time	Most of the time	Slightly more than half the time	Slightly less than half the time	Some of the time	At no time
			Diagnostic demarcation line ↑					
	1	Have you felt low in spirits or sad?	5	4	3	2	1	0
	2	Have you lost interest in your daily activities?	5	4	3	2	1	0
	3	Have you felt lacking in energy and strength?	5	4	3	2	1	0
Highest score for DSM-IV major depression	4	Have you felt less self–confident?	5	4	3	2	1	0
	5	Have you had a bad conscience or feelings of guilt?	5	4	3	2	1	0
	6	Have you felt that life wasn't worth living?	5	4	3	2	1	0
	7	Have you had difficulty in concentrating, e.g. when reading the newspaper or watching television?	5	4	3	2	1	0
Highest score	8a	Have you felt very restless?	5	4	3	2	1	0
	8b	Have you felt subdued or slowed down?	5	4	3	2	1	0
	9	Have you had trouble sleeping at night?	5	4	3	2	1	0
Highest score	10a	Have you suffered from reduced appetite?	5	4	3	2	1	0
	10b	Have you suffered from increased appetite?	5	4	3	2	1	0

Total Score (item 1 - 10) : =____ +____ +____ +____ +___= ☐ ☐

DSM-IV diagnosis _____

Major Depression Inventory (MDI):

Scoring Instruction

A: As a diagnostic instrument for DSM-IV major depression

The diagnostic demarcation line indicates at which point a symptom is severe enough to be used in the DSM-IV algorithm of major depression. Thus, the first three symptoms should have been present at least "most of the time" during the past two weeks, while the other symptoms should have been present "more than half" of the period. For symptoms 4 and 5, only the highest score should be used, as the DSM-IV contains only 9 of the 10 MDI symptoms and as symptoms 4 and 5 belong to the same category in DSM-IV. For symptoms 8 and 10, only the one of the two alternatives (a or b) with the highest score is considered.

Major depression is diagnosed if 5 or more of the 9 symptoms (items 4 and 5 combined) have been present in the past two weeks and if symptom 1 or symptom 2 are included in these 5 symptoms.

Reference:

Bech P, Rasmussen N-A, Olsen LR, Noerholm V, Abildgaard W. The sensitivity and specificity of the Major Depression Inventory, using the Present State Examination as the index of diagnostic validity. J Affect Disord 2001; 66: 159-164

B: As a depression rating scale

As a severity measure, the MDI score ranges from 0 to 50, since each of the 10 items can be scored from 0 (at no time) to 5 (all the time). Again, for items 8 and 10, alternative a or b with the highest score is considered.

Mild depression	MDI total score of 20 to 24
Moderate depression	MDI total score of 25 to 29
Severe depression	MDI total score of 30 or more

Reference:

Olsen LR, Jensen DV, Noerholm V, Martiny K, Bech P. The internal and external validity of the Major Depression Inventory in measuring severity of depressive states. Psychol Med 2003; 33, 351-356

9.2 APPENDIX B. DSM -5 CRITERIA FOR ANXIOUS DISTRESS AND CORRESPONDING QUESTIONS USED FROM SCALES IN MENTAL HEALTH IN THE PART STUDY TO ASSESS ANXIOUS DISTRESS

DSM-5 criteria for anxious distress [1]	Scale	Question on Symptom
Feeling keyed up or tense.	Psychological well-being scale[2]	How many times have you felt calm and relaxed during the past week? Those who replied “never” or “sometimes” were regarded as having anxious distress symptom
Feeling unusually restless.	Major depression inventory [3]	How many times have you felt very restless in past 2 weeks? Those who answered “all the time”, “most of the time” or “slightly more than half of the time” were regarded as having anxious distress symptom
Difficulty concentrating because of worry.	Major depression inventory	How many times have you had difficulty in concentrating in past 2 weeks? Those who answered “all the time”, “most of the time” or “slightly more than half of the time” were regarded as having anxious distress symptom
Fear that something awful may happen.	Symptoms of anxiety during the past 30 days.[4]	How much in the past 1 month have you experienced fear of dying? Those who answered “much” or “very much” were regarded as having anxious distress symptom
Feeling that the individual might lose control of himself or herself.	Symptoms of anxiety during the past 30 days	How much in the past 1 month have you had fear of losing control? Those who answered “much” or “very much” were regarded as having anxious distress symptom

[1] Anxious distress is defined as the presence of at least two of the following symptoms during the majority of days of a major depressive episode or persistent depressive disorder (dysthymia). In the present study severity was classified as; mild: two symptoms, moderate: three symptoms, moderate-severe: four or five symptoms; and severe: four or five symptoms and with motor agitation. (http://dsm.psychiatryonline.org//, doi: 10th April 2015)

[2] Bech, P., Gudex, C., Staehr Johansen, K. (1996). The WHO (Ten) Well-Being Index: Validation in Diabetes. Psychother Psychosom, 65, 183-190.

[3] Bech, P., Wermuth, L. (1998). Applicability and validity of the Major Depression Inventory in patients with Parkinson´s disease. Nord J Psychiatry, 52, 305-309

.[4] Sheehan, D. V. (1983). The anxiety disease (pp 124-129). New York: Charles Scribners Sons

9.3 APPENDIX C. SWEDISH SCALE OF PERSONALITY REFLECTING NEUROTICISM; MEAN AND T SCORE

Scale	Question number in SSP	Question	Mean (SD) score of individual questions[1]	Mean(SD) score of scale	Mean (SD) t-score of scale [3]
Somatic Trait Anxiety (STA)					
	1	Quite often, I found myself without reason clenching my jaw.	1.8 (0.97)	1.7 (0.5)	47.9 (9.7)
	14	I often feel restless, as if I wanted something without knowing what.	2.0 (0.9)		
	27	I often feel stiff and tense the body	2.0 (0.9)		
	40	Sometimes, my heart thumps hard or beat irregularly without tangible reason.	1.5 (0.8)		
	53	I can suddenly start sweating for no particular reason.	1.5 (0.8)		
	66	I jerk violently to unexpected sounds.	1.9 (0.9)		
	79	Sometimes I get a feeling of not getting enough air to breathe.	1.4 (0.8)		
Stress Susceptibility(SS)					
	3	I can too easily get tired and stressed.	2.2 (0.8)	2.0 (0.4)	51.0 (8.1)
	-16[2]	I can easily be disturbed when I'm doing a job.	2.0 (0.7)		
	29	In order to get anything done, I have to consume more power than most.	1.5 (0.7)		
	-42	I tend to concentrate even if the surroundings are distracting	2.2 (0.7)		
	55	I get easily stressed when I am asked to speed up my work.	2.0 (0.8)		
	-68	I feel calm and confident even if I have to face new challenges.	2.2 (0.7)		
	81	I find that I have less energy than most of my acquaintances.	1.6 (0.8)		
Embitterment(E)					
	9	I have had it quite difficult in life	1.8 (0.8)	1.6 (0.4)	46.5 (9.9)
	22	I never seem to be able to avoid getting into jams.	0.6 (1.3)		
	35	I have often got into trouble, even though it was not my fault.	1.3 (0.6)		

48	It looks as if I would never get any chance to get anywhere in life.	1.5 (0.7)
61	I seem to more often than others do things that I later regret	1.4 (0.6)
74	It happened that I envied people who have been lucky in life	2.1 (0.9)
87	I feel often like I did something bad or wrong.	1.5 (0.7)

[1] Each item is given as a statement with a four-point response format, ranging from 1 to 4, 1 point for the "disagree" and so on to 4 points for the "agree".

[2] Minus in front of the question number means the scoring was reversed. This applies to the item 7, 16, 30, 38, 42, 68, 85, and 86

[3] t-scores have been calculated according to Gustavsson, J.P., et al., Swedish universities Scales of Personality (SSP): construction, internal consistency and normative data. Acta Psychiatr Scand, 2000: 102(3).

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