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Doctoral thesis

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Norwegian University of Science and Technology
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Summary

Cardiovascular disease (CVD) is one of the leading causes of death and disability in the world. Much knowledge exists about the physical risk factors of CVD, and there is a growing field of knowledge about the psychological risk factors of CVD. Although depression and anxiety has received the most attention, dispositional factors like personality have also been linked to risk of CVD. The overall goals of this thesis were to investigate the effects of psychological variables on CVD risk, and whether they are sex-specific. This thesis is premised on four papers. One was based on the U.S. MrOS study, a longitudinal cohort of elderly men. Two were based on a population cohort from the Norwegian HUNT Study. The remaining paper was a literature review. The aim of Paper I was to investigate anxiety as a risk marker of CVD independent of depression. The aim of Paper II was to summarise the findings of recent meta-analyses and large-scale studies that investigated the effect of anxiety on CVD while adjusting for depression, and to suggest potential explanations for the conflicting findings in the field. The aim of Paper III was to investigate the association between the use of antidepressants and myocardial infarction (MI), and whether this association was sex-specific. The aim of Paper IV was to investigate the personality traits of extraversion and neuroticism and their association with MI and stroke, and whether these associations were sex-specific.

To briefly summarise the findings, anxiety was associated with CVD, albeit to a lesser degree than depression, and did not seem to be a CVD risk marker independent of depression. Antidepressant use was associated with a reduced risk of MI for both men and women. Neuroticism was associated with an increased risk of MI in men, while extraversion was associated with an increased risk of stroke in women. There were no sex differences in the effects of antidepressant use. The implications of this thesis are that anxiety is not an independent risk marker of CVD, and that personality may explain some effects of depression and anxiety on CVD. Antidepressants seem to be safe to use in relation to CVD risk, and there does not seem to be differences among men and women in this regard. When studying the various CVD endpoints such as MI and stroke, heterogeneous effects of psychological variables were observed, which suggests that it is important to investigate the specific CVD sub-groups separately.

Sammendrag

Hjerte- og karsykdommer (HKS) er blant de ledende årsakene til død og nedsatt funksjonsevne i verden. Det eksisterer mye kunnskap om de fysiske risikofaktorene til HKS, og et voksende forskningsfelt søker også kunnskap om de psykologiske risikofaktorene. Angst og depresjon har fått mest oppmerksomhet, men også disposisjonelle faktorer som personlighet har blitt relatert til risiko for å utvikle HKS. Hovedmålet til denne avhandlinga var å undersøke effektene av psykologiske variabler på risiko for å utvikle HKS og hvorvidt disse effektene er kjønnsspesifikke. Avhandlinga består av fire forskningsartikler. En er basert på MrOS-studien fra USA, hvor en gruppe eldre menn blei fulgt over lengre tid. To er basert på den norske HUNT-studien, som fulgte innbyggerne i Nord-Trøndelag over flere tiår. Den gjenværende artikkelen er en oversiktsstudie av forskningslitteraturen. Målet med artikkel I var å undersøke om angst er en risikomarkør for HKS uavhengig av depresjon. Målet med artikkel II var å oppsummere funna i de nyeste meta-analysene og de store studiene som har undersøkt effekten av angst på HKS samtidig som de justerte for effekten av depresjon. I tillegg til dette foreslo vi mulige forklaringer på de motstridende funna i forskningsfeltet. Målet med artikkel III var å undersøke sammenhengen mellom bruk av antidepressiva og forekomst av hjerteinfarkt, samt hvorvidt denne sammenhengen var kjønnsspesifikk. Målet med artikkel IV var å undersøke personlighetstrekkene

ekstraversjon og nevrotisisme og deres forhold til hjerteinfarkt og slag, samt hvorvidt disse forholda var kjønnsspesifikke.

Oppsummert er funna at angst i mindre grad enn depresjon var assosiert med HKS, og angst så ikke ut til å være en risikomarkør for HKS uavhengig av depresjon. Bruk av antidepressiva var forbundet med en redusert risiko for hjerteinfarkt hos både menn og kvinner. Nevrotisisme var forbundet med en økt risiko for hjerteinfarkt hos menn, mens ekstraversjon var forbundet med en økt risiko for slag hos kvinner. Det var ingen kjønnsforskjeller i effekten av antidepressiva. Implikasjonene fra avhandlinga blir dermed at angst ikke er en uavhengig risikomarkør for HKS. Og at personlighet kan forklare noe av den effekten som har blitt observert av depresjon og angst på HKS. Antidepressiva virker trygge med tanke på risiko for HKS, og det ser ikke ut til å være forskjeller mellom menn og kvinner her. Når man undersøker de ulike formene for HKS, slik som hjerteinfarkt og slag, finner man til dels svært ulike effekter av psykologiske variabler. Dette tyder på at det er viktig å undersøke de spesifikke HKS-undergruppene separat istedenfor å slå dem sammen.

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Papers included in thesis

This thesis is based on the following four papers:

(I) Karlsen, H. R., Saksvik-Lehouillier, I., Stone, K. L., Schernhammer, E. S., Yaffe, K., & Langvik, E. (2020). Anxiety as a risk factor for cardiovascular disease independent of depression: A prospective examination of community-dwelling men (The MrOS study). *Psychology & Health. 36*(2), 148–163. https://doi.org/10.1080/08870446.2020.1779273

(II) Karlsen, H. R., Matejschek, F., Saksvik-Lehouillier, I., & Langvik, E. (2021). Anxiety as a risk factor for cardiovascular disease independent of depression: A narrative review of current status and conflicting findings. *Health Psychology Open, 8*(1), 1–7. https://doi.org/10.1177/2055102920987462

(III) Karlsen, H. R., Langvik, E., & Løchen, M. L. (In review). Antidepressant use and risk of myocardial infarction. A longitudinal investigation of sex-specific associations in the HUNT study. *Psychosomatic Medicine*.

(IV) Karlsen, H. R., & Langvik, E. (Submitted). Sex-specific psychological risk profiles of CVD in the HUNT study: The role of neuroticism and extraversion. *Psychology & Health.*

Figures included in thesis

Abbreviations

CER	Cerebrovascular disease
CHD	Coronary heart disease
CVD	Cardiovascular disease
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5^{th} edition
DÅR	Norwegian Cause of Death Registry
EPQ	Eysenck Personality Questionnaire
FFM	Five-Factor Model
GADS	Goldberg Anxiety and Depression Scales
HADS	Hospital Anxiety and Depression Scales
HR	Hazard ratio
HRV	Heart rate variability
HUNT	Trøndelag Health Study
ICD	International Classification of Diseases
MI	Myocardial infarction
MrOS	The Osteoporotic Fractures in Men Study
NorPD	Norwegian Prescription Database
OR	Odds ratio
REK	Regional Committee for Research Ethics
SD	Standard deviation
SSRI	Selective serotonin reuptake-inhibitor
TCA	Tricyclic antidepressant

1. Introduction

One of the major challenges from a global health perspective is cardiovascular disease (CVD). The total global burden of CVD has increased from 1990 to 2019 (Vos et al., 2020), but this is partially due to population growth and ageing. When adjusting for these factors, the burden has in fact slightly decreased during that period. Despite this, CVD remains one of the most common causes of death and disability globally (Vos et al., 2020). It is still important to focus more on how to reduce the number of CVDs. In this endeavour, researchers have increasingly investigated psychological factors that could potentially cause CVD. Depression has repeatedly been shown to be associated with increased risk of CVD (Gan et al., 2014; Wu & Kling, 2016). Anxiety has also been suggested as a potentially important factor in explaining the development of CVD (Batelaan et al., 2016). More broadly, a few studies have suggested that personality is important to consider when looking at CVD (Sahoo et al., 2018). Recent international CVD prevention guidelines have explicitly focused on an interdisciplinary approach that considers psychosocial factors, among other considerations (Visseren et al., 2021). This study of the effects of psychological factors on the aetiology, diagnosis, treatment and prevention of CVD is called psychocardiology. Understanding the effects that these psychological variables have on CVD is important to further our understanding of the development and progression of one

of the most destructive diseases in terms of mortality, years lived with disability and societal costs.

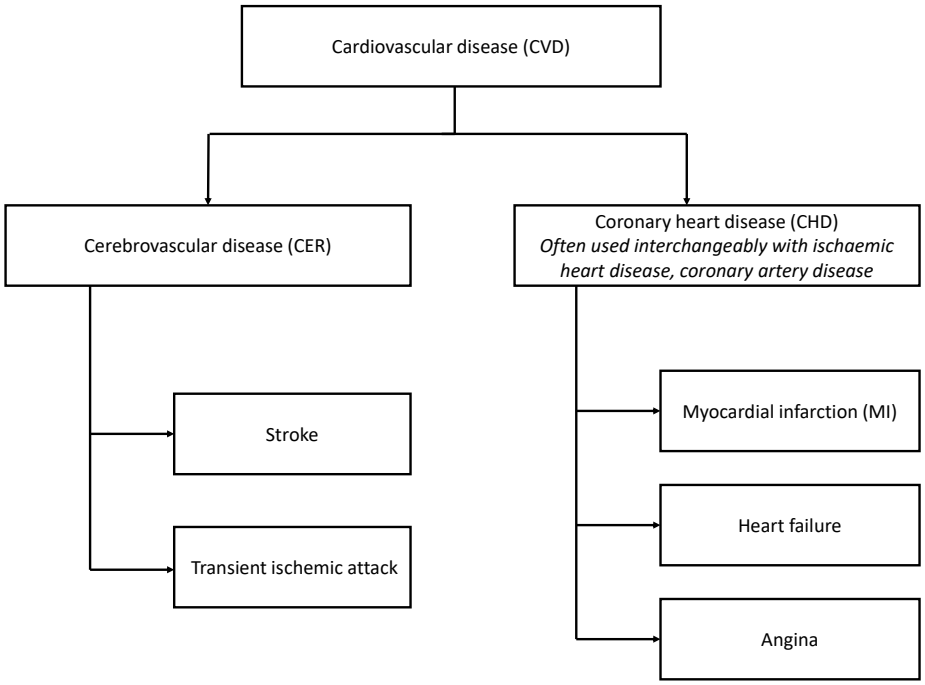
1.1 Cardiovascular disease

Formally, CVD is any disease of the heart and blood vessels, and it includes a broad range of diseases with heterogeneous aetiologies and presentations, including a number of sub-types. The following is a brief description of the types of CVD that have been the most thoroughly investigated in relation to psychological risk factors (see Figure 1.1 for a presentation of the hierarchy). Coronary heart disease (CHD, also known as coronary artery disease or ischemic heart disease) is caused by issues with the blood vessels supplying the heart. These issues can arise as a result of atherosclerosis, which is the build-up of plaque in the heart muscles that reduces blood flow (Xu et al., 2015). A sub-type of CHD is myocardial infarction (MI), which is classified as either ST-elevation MI or non-ST-elevation MI, depending on whether or not the segment between the S and T waves of an electrocardiography is elevated. If the blood flow to the brain is disrupted, this may result in cerebrovascular disease (CER). Stroke is a type of CER that is caused by an occlusion or haemorrhage in blood vessels supplying the brain (Lo et al., 2003).

1.1.1 Approaches to studying cardiovascular disease as an endpoint

There are two common methodologies in disease research: aetiologic and prognostic approaches (Tripepi et al., 2008). In the aetiologic approach, researchers attempt to determine causal relationships between risk markers and disease outcomes. Adjusting for known confounders is an important part of this research, to determine whether an observed relationship is actually caused by a confounder. A risk marker here represents a variable that has been shown to correlate with the disease outcome, but whether it has a causal effect on the outcome is not yet known. If aetiologic re-

Figure 1.1: Hierarchical structure of CVD and its sub-groups with examples within each sub-group.



search can determine a causal effect of the variable, it is considered a risk factor. The prognostic approach attempts rather to predict the probability of a disease outcome. Here, causality and confounding are less important. Risk markers are entered into a statistical model on the basis of their ability to predict the outcome, regardless of the causal or confounding effect.

In practice, researchers typically use an aetiologic approach to refer to a sampling strategy in which a healthy sample is followed over time and incidences of a disease are recorded (Langvik & Nordahl, 2014; Nicholson et al., 2006). Participants with previous instances of the disease are then excluded or the condition is statistically adjusted for. Relevant risk factors, markers and confounders are measured at baseline and potentially at more times. Prognostic strategies, on the other hand, often follow a sample recruited because they already have the disease. Then they are followed over

time to see how many experience a new disease event or mortality. In the latter case, the term prognostic is used to mean the study of the progress of a disease (Kent et al., 2020).

The prognostic approach is more descriptive than the aetiological approach. It is also simpler, in that it only needs to establish a correlation between a variable of interest and the disease endpoint. This is valuable knowledge, as the presence of a given variable is associated with an increased risk of developing the disease. An aetiologic approach might show that the variable in itself is not actually responsible for the increased risk of disease — a third, confounding variable is associated with the first variable and is actually responsible for causing the increased risk of the developing the disease. Regardless of the aetiology of the disease, if a risk marker has prognostic value, it would be beneficial to screen for it, as this will allow a health care practitioner to determine whether the patient is a risk of the disease. Knowledge of the aetiology of the disease would inform the practitioner whether treating the risk marking variable itself, or if it is simply related to a third variable that causes the changes since in both the first variable and the disease outcome.

In terms of CVD, there exists a large amount of knowledge about the risk factors and risk markers (Visseren et al., 2021). It is well established that certain variables like age, high blood pressure and diabetes mellitus have a causal effect on the risk of developing CVD — that they are risk factors. As CVD is still among the most common causes of death and disability in the world, researchers have turned to psychological variables as potential risk factors. Depression has repeatedly been shown to be a risk marker for CVD in large studies (Harshfield et al., 2020; Park et al., 2020; Sun et al., 2016; Whang et al., 2009) and meta-analyses (Gan et al., 2014; Wu & Kling, 2016). Some have even concluded that it has a causal effect on the risk of developing CVD, labelling it a risk factor (O'Neil et al., 2016; Sun et al., 2016). Another, related mental disorder that has received attention in this regard, is anxiety.

While several studies have determined that anxiety is linked to CVD (Batelaan et al., 2016; Nicholson et al., 2006), a common criticism is that they have not adjusted for the confounding effect of depression (Batelaan et al., 2016). This exemplifies the challenge of establishing causality and understanding whether a variable is an aetiologic risk factor: Despite determining that anxiety is associated with an increased risk of CVD in the presence of traditional risk factors (i.e., age, diabetes, high blood pressure and cholesterol levels), an entirely different factor — in this case, depression — could be responsible for the association between anxiety and CVD.

From a philosophical perspective, the best a researcher can aspire to is to *attempt* to determine the aetiologic value of various psychological factors. To *succeed* would require the measurement and adjustment of all possible risk markers and factors, even those that are currently unknown. In more practical terms, researchers settle for adjusting for known risk factors, and declare the variable of interest to have aetiologic value if it subsequently remains a cause of change in CVD risk. In this spirit, the aim of this thesis is to enhance the extant body of knowledge regarding the aetiological value of psychological risk factors for CVD.

Studies in this field typically study samples initially free of CVD, or samples where individuals with previous instances of CVD are excluded. Endpoints are then called incident CVD, meaning that this is the first CVD event that the individuals are experiencing. Alternatively, researchers can recruit individuals who have already experienced a CVD event. In this case, the endpoint is recurrent CVD, as the individuals are followed until they experience a subsequent CVD event. Studies of post-CVD samples are limited in generalisability, as having an initial CVD event increases the risk of subsequent ones (Visseren et al., 2021). Additionally, CVD is known to increase the risk of developing both anxiety and depression (Pogosova et al., 2015; Thombs et al., 2006). There is thus an issue of potential bidirectionality of anxiety and depression with CVD in these cases (Pogosova et al., 2015), as it is unknown

whether the depression or anxiety causes CVD, or whether the CVD was causes by previous CVD with also causes the depression or anxiety.

1.2 Psychological factors in cardiovascular disease

Researchers have identified several factors that directly influence an individual's risk of developing CVD (Visseren et al., 2021). Among the most common are diabetes mellitus, high blood pressure and smoking cigarettes. Recent studies have started to focus on psychological factors. The idea that the brain and the heart affect one another is not new, with ancient Greek philosophers first proposing a link between the heart and soul (Esler & Schwarz, 2015). However, later medical models in the early modern period would create a clear divide between the mental and physical diseases (Alvarenga & Byrne, 2015). Contemporary medical models again feature an incorporated view of the complex relationship between the physical and mental systems and diseases. Two psychological variables that have been suggested as having an effect on CVD are depression and anxiety.

1.2.1 Depression and anxiety

Globally, anxiety and depression are among the most common mental disorders (Vos et al., 2020). They are also comorbid and predictive of each other (Brown et al., 2001; Jacobson & Newman, 2017). Depression and anxiety can be considered as disorders, but they can also be considered as dispositions. Those who have a too large number of symptoms are classified as clinical, while others have subclinical levels of anxiety of depression. Everyone has some degree of anxiety and depression in terms of symptom level (Thurston et al., 2013), but not everyone has it too such a degree that they will develop a corresponding disease.

Depression is a condition characterised by depressed mood and anhedonia (reduced ability to feel pleasure) primarily, though also commonly by reduced appetite,

insomnia and fatigue (Malhi & Mann, 2018). If the depression is severe enough, it is categorised as clinical depression. The most common of these is major depressive disorder, which can be diagnosed following a major depressive episode lasting at least two weeks, according to the DMS-5 (American Psychiatric Association, 2013). Depression may also be subclinical if the symptoms are not severe enough to produce a diagnosis. Symptom level depression can thus be considered a continuum, ranging from the absence or a low level of depressive symptoms to a high level of symptoms.

In 2019, the global prevalence of depression was 280 million cases (i.e., 3.4% of the world's population), with an incidence of 290 million (3.6%) (Global Burden of Disease, 2020b). The prevalence is higher in women (4.2%) than in men (2.7%). Depression is most prevalent in younger individuals, with many experiencing their first episode in adolescence, and most experiencing it before age 40 (Malhi & Mann, 2018). Between 1990 and 2019, depressive disorders went from being the 19th to 13th leading causes of disability-adjusted life-years globally (Vos et al., 2020). For individuals aged 10 to 49 they are among the top six causes.

Anxiety is a feeling of persistent fear and unpredictability directed towards events, objects or the future (Thurston et al., 2013). While the experience of anxiety is symptomatic of the human condition, pathological levels can lead to a clinical diagnosis. The most common anxiety disorder is general anxiety disorder, defined as having excessive anxiety and worry about events and activities (American Psychiatric Association, 2013). Other forms of anxiety disorders also exist, like panic disorder, or specific phobias. The global prevalence of anxiety was 301 million cases globally (Global Burden of Disease, 2020a), and it is more prevalent in women (4.7%) compared to men (2.9%). Similar to depressive disorders, anxiety disorders also became a more prominent leading cause of disability-adjusted life years globally, from 34th in 1990 to 24th in 2019 (Vos et al., 2020). The failure to properly understand and handle anxiety has been offered as an explanation for why CVD is still the main cause of

death (Alvarenga & Byrne, 2015).

A diagnosis of anxiety or depression usually requires a trained health care professional to interview the patient. This is resource intensive. To make the process easier, anxiety and depression inventories have been invented. These consist of items that the patient themselves or the health care professional fill out. Examples are the Goldberg Anxiety and Depression Scales, or the Hospital Anxiety and Depression Scales (D. Goldberg et al., 1988; Zigmond & Snaith, 1983). The inventories usually include some score thresholds above which a person is considered a likely clinical case. Instruments can be used as a screening technique, which then allows the health care professional to verify the diagnosis. In research, the cut-offs are often treated as indicators of depression or anxiety directly. Alternatively, the scores may be used as continuous measures of symptom severity for these disorders.

The effect of depression and anxiety on CVD

Initial evidence of an association between depressive mood and the heart was seen in discovery of takotsubo syndrome, also known as stress cardiomyopathy (Tofield, 2016). It is a sudden weakening of the heart muscle that develops as a result of extreme stress and has often been seen in the elderly after their long-term partner die (Sealove et al., 2008). Several recent meta-analyses have also directly linked depression to CVD: Wu and Kling (2016) found that depression was associated with increased risk of MI and death due to CHD; Correll et al. (2017) concluded that individuals with major depressive disorder were at higher risk for CHD and CVD-related death; Harshfield et al. (2020) linked depression symptoms to CVD incidence; and Smaardijk et al. (2019) found an association between depression and CHD.

Reports from the Netherlands Study of Depression and Anxiety indicate that participants with clinical depression or anxiety were more likely to have subclinical atherosclerosis than healthy controls (Seldenrijk et al., 2010). Building on this, a later

paper on the same study found that that anxiety sensitivity (having perceptions that bodily functions are harmful in physical, mental or social ways) was associated with subclinical CVD, while depression sensitivity (aggression, rumination, hopelessness) was not (Seldenrijk et al., 2013). The authors argued that anxiety and depression sensitivity showed less overlap and heterogeneity than clinical anxiety and depression. Hence, this indicated that anxiety could be responsible for some of the effects observed of depression on CVD.

Several meta-analyses have been conducted to evaluate the association between anxiety and CVD: Roest et al. (2010) observed that anxiety seemed to be an independent risk factor for CHD and cardiac mortality; Emdin et al. (2016) concluded that anxiety was associated with increased risk of cardiovascular mortality, CHD, stroke and heart failure; Pérez-Piñar et al. (2017) found that anxiety disorders were associated with an increased risk of stroke and presented evidence suggesting that the risk was greatest within three years of an anxiety disorder diagnosis, and that the severity of the disorder affected the risk; Batelaan et al. (2016) found that anxiety was associated with increased risk of CVD when adjusting for known risk factors and depression, suggesting that anxiety was a cause of CVD; and Smaardijk et al. (2019) found that anxiety was related to CHD. Meta-analyses focusing on specific categories of anxiety disorders have also found effects on CVD. Tully et al. (2015) reported that panic disorder was associated with increased risks of CHD, MI and major adverse cardiovascular events. Edmondson et al. (2013) found that post-traumatic stress disorder was independently associated with increased risk for CHD

The weight of the evidence is now strong enough that researchers consider depression a causal factor in CVD development (Byrne et al., 2015). Despite this, a remaining question is how depression influences CVD. This can happen directly on biological processes, or more indirectly via comorbid conditions or behaviours. In the following section, some of the proposed pathways are discussed.

Pathways from anxiety and depression to CVD

Inflammation is a likely pathway from depression to CVD. Inflammation is indicated by the presence of sub-acute elevated levels of markers like C-reactive protein and interleukin-6 (Danesh, 2000; Khandaker et al., 2020). Short-term inflammation is part of healthy bodily functioning, but if the inflammation is not resolved, it can lead to chronic, low-grade inflammation (Lorenzatti & Servato, 2019). This type of inflammation increases the risk of atherosclerosis, which in turn can lead to CVD. Inflammation also increases the risk of developing depression as well as worsens the prognosis of existing depression (Berk et al., 2013; Chu et al., 2021; Pasco et al., 2010). The causal paths between inflammation, depression CVD are not fully established, and there is likely bidirectionality involved (Seligman & Nemeroff, 2015). Meaning that inflammation can lead to both depression and increased CVD risk, and the presence of depression can then further increase the CVD risk. Anxiety has also been associated with inflammation, though the effects observed have not been as strong nor clear as for depression (Celano et al., 2018; Ye et al., 2021).

Depression and anxiety can alter activity in the sympathetic and parasympathetic nervous system (Chalmers et al., 2014; Hammel et al., 2011; Kemp et al., 2010; Ryan, 2020). Meta-analyses have shown that individuals with depression or anxiety have lower heart rate variability (HRV) than healthy controls (Chalmers et al., 2014; Kemp et al., 2010). HRV refers to variations in consecutive beat-to-beat intervals of the heart (Sammito et al., 2015). This variation can be measured using electrocardiography and results in several different parameters spread along three domains: the frequency, time and non-linear domains. HRV reflects the level of sympathetic and parasympathetic nervous system activity. Low HRV increases the risk of CVD by increasing the sympathetic nervous activity and decreasing the parasympathetic nervous system activity (Hillebrand et al., 2013; Sammito et al., 2015). In this way, anxiety and depression can affect CVD risk via autonomic dysfunction, in the form

of increased sympathetic activity and decreased parasympathetic activity (Hammel et al., 2011; Ryan, 2020). Stressful events can cause sensitisation of the cardiac sympathetic nerves, leading to cardiovascular hyperreactivity. In such cases, the cardiovascular system reacts too strongly to behavioural stimuli, by increasing the heart rate and blood pressure more than normal (Rozanski et al., 1999).

Depression is a risk factor for hypertension (Meng et al., 2012), while anxiety is associated with hypertension (Pan et al., 2015). Hypertension is chronic elevated blood pressure (Poulter et al., 2015), and an independent risk factor for CVD (Visseren et al., 2021). A meta-analysis by Busch et al. (2017) found that rumination increased cardiac reactivity. Specifically, both angry and sad rumination had large, significant effects on heart rate as well as diastolic and systolic blood pressure. The largest effects were seen of angry rumination on heart rate. It has been suggested that anxiety and depression can cause ischemia via coronary artery vasospasm (Hung et al., 2019; Levine et al., 2021). Another pathway from depression to CVD might be via platelet activity. Depression has been linked to increased platelet activation and reactivity (Bruce & Musselman, 2005; Seligman & Nemeroff, 2015).

Both anxiety and depression increase the risk of smoking (Fluharty et al., 2017; Jiang et al., 2014) and obesity (Amiri & Behnezhad, 2019; Mannan et al., 2016). Individuals with depressive disorders are more likely to have poor adherence for cardiovascular medicine (Goldstein et al., 2017). Researchers have even found a dose-response relationship between depression and cardiovascular medicine adherence (Rieckmann et al., 2006). It remains unclear whether non-adherence is typical with anxiety (DiMatteo et al., 2000).

Finally, behavioural and biological factors may bi-directionally influence one another. Reduced physical activity or non-adherence of certain medication can increase inflammation, which in turn can increase depressive symptoms (Cohen et al., 2015). In the same vein, Duivis et al. (2013) found that when adjusting for unhealthy lifestyle

factors like body mass index, smoking and alcohol intake, the initially significant association of inflammation with depression and anxiety was heavily attenuated.

Personality traits, especially neuroticism, has been associated with anxiety and depression disorders (Bienvenu et al., 2004). One study found that depression was linked to increased risk of stroke, but only for individuals low in neuroticism (Marijnissen et al., 2014). The low number of studies on this topic, and the results of these few studies, suggests a need to focus on the effect of personality traits on CVD.

1.2.2 Personality

Personality traits are individual differences in consistent patterns of thinking, feeling or behaving (Johnson, 1997). While multiple personality taxonomies exist, few have acquired the enduring presence of the Five Factor Model (FFM). The result of more than 50 years of iterative work by leading psychological researchers (Costa & McCrae, 1995; Digman, 1990; L. R. Goldberg, 1990), the FFM consists of five personality traits, also known as the Big Five: neuroticism, extraversion, conscientiousness, agreeableness and openness to experience. The FFM has been criticised for not being universal to all humans (Gurven, 2018). It is most consistent in WEIRD (White, educated, industrialised, rich, democratic; Henrich et al., 2010) populations, and fails to replicate in smaller, rural societies (Gurven, 2018). Despite this, it is likely the most well-documented and researched personality taxonomy.

Another personality taxonomy is that of H. J. Eysenck (1975), which includes the three traits of extraversion, neuroticism and psychoticism. Although Eysenck's taxonomy decreased in popularity and use after the introduction of the FFM, it is notable for partially overlapping with the FFM since extraversion and neuroticism are found in both taxonomies. Neuroticism is characterised by having anxious and depressive thoughts, being hostile, worrying and feeling vulnerable and self-conscious (Almas et al., 2017). Extraversion is characterised by being warm, sociable, assertive

and active, experiencing positive emotions and excitement seeking (McCrae & Costa, 2010). No single model of personality traits can hope to capture all the variance in human personality (Johnson, 1997); at most, they can hope to present a reasonably complex model that will capture a large amount of variance.

The central unit of analysis for personality is the trait, though personality is also often operationalised as types, which are patterns of traits (Johnson, 1997). Traits and types can be measured as continuous dimensions, or as discrete categories. The former is typical for traits and the latter is typical for types. Accordingly, from the trait approach, an individual may be high or low in extraversion, or anywhere in between. In contrast, from a type approach, the individual is either an introvert or an extravert.

Personality and CVD

Most of the research published on the links between CVD and personality is done on personality types rather than traits. In the 1950s, researchers described the association between a personality type and the incidence of CHD (Friedman, 1959). The personality type would subsequently be called type A. (The type A construct has variously been referred to as a behaviour or as a personality. In this thesis, the term *personality* is used to describe it, as this is in line with the previous definition of personality as a pattern of thinking, feeling and behaving.) An individual characterised as type A experiences higher levels of competitive achievement motivation, sense of time urgency and hostility. After a series of studies initially found significant links between type A personality and CVD, later studies were less clear (Dimsdale, 1988). The type was also criticised for being too heterogenous, and for inconsistencies in how to measure it (Suls & Wan, 1989).

In the 1990s, a new personality type gained popularity, named type D because it reflected a distressed type. Several influential papers found that type D personality had a significant effect on the risk of MI and heart disease (Denollet et al., 1996;

Denollet et al., 1995). Type D personality is characterised by above the median scores on social inhibition and negative affectivity (Denollet & Brutsaert, 1998).

Type D research has received significant criticism since the first major studies were performed in the 1990s. Coyne and colleagues (Coyne et al., 2011; de Voogd et al., 2012) have focused their critiques on several points: Most studies that endorse a link between type D personality and CVD came from the same research group centred around Tilburg University. These studies were underpowered, featuring too few CVD endpoints to justify the statistical modelling performed. Type D was operationalised as a category instead of as a continuous score.

Large scale studies performed by researchers unaffiliated with Tilburg University's research group have tended to report null findings (Coyne & de Voogd, 2012; Coyne et al., 2011; Meyer et al., 2014), while a meta-analysis and review concluded that earlier studies had overestimated the prognostic value of Type D personality in predicting mortality among patients with CVD (Grande et al., 2012). A simulation study also revealed issues of inflated false positive rates with previous strategies for operationalising type D personality (Lodder, 2020). With this in mind, there are methodological reasons for being sceptical of findings related to type D personality.

When type A fell out of favour as a risk factor of CVD, part of the reason was that certain aspects of the personality type seemed to account for most of the observed effect (Bishop, 2015). That aspect was the trait hostility. Similarly, in research on type D personality, focus turned to the two traits that made up the personality type: negative affect and social inhibition. By dichotomising these two traits, and combining them, researchers were losing information about the component-traits of type D personality and the opportunity to look at these traits independently (Bishop, 2015).

Researchers have found that type D sub-scales are strongly related to personality traits — particularly extraversion and neuroticism which together describe about half of the variance in a type D factor (De Fruyt & Denollet, 2002). Thus indicating that

some of the findings from type D may be applicable to these traits. Type D is characterised by social inhibition and negative affectivity (Denollet et al., 1996). Social inhibition is strongly correlated with introversion and negative affectivity with neuroticism (De Fruyt & Denollet, 2002). Other studies have found that the FFM traits are better able to predict health related variables and behaviour than type D (Horwood & Anglim, 2017).

Jokela et al. (2014) pooled the data from several studies and found that extraversion increased the risk of stroke mortality, while neuroticism increased the risk of CHD mortality. Conscientiousness reduced the risk of both CHD and stroke. Shipley et al. (2007) found that neuroticism was related to CVD mortality. Initially significant effects of extraversion disappeared after adjustment for relevant covariates. Positive emotions, one of the core facets of extraversion (McCrae & Costa, 2010), has been shown to be protective against CHD, even when adjusting for depression (Davidson et al., 2010).

Several studies have indicated that personality traits have indirect effects on CVD: One study found that neuroticism increased the risk of CVD and had a synergistic interaction with depression (Almas et al., 2017). In a study of older individuals, neuroticism was not an independent predictor of stroke when adjusting for the effects of depression (Marijnissen et al., 2014). When looking only at participants without a history of cardiac disease, depression and neuroticism interacted in such a way that depression only predicted stroke in those low in neuroticism. Another study found that neuroticism potentially explains some of the comorbidity of CVD and depression (Čukić & Bates, 2015). Finally, Hagger-Johnson et al. (2012) found that women with low SES and high neuroticism face an increased risk of CVD mortality, while women with high SES and high neuroticism face a decreased risk of CVD mortality.

A meta-analysis found that rumination affects cardiac outcomes (Busch et al., 2017). Angry rumination had a bigger effect than sadness rumination. Rumination

affected heart rate, diastolic and systolic blood pressure, though the latter two more strongly. This suggested one pathway in which depressive and hostile thoughts could affect CVD risk: Repeated cardiovascular activation because of rumination could lead to autonomic dysregulation. Studying personality, physical activity and markers of inflammation, Graham et al. (2018) found that physical activity mediated the relationship between personality and markers of inflammation. Specifically, neuroticism was significantly related directly to inflammation, while physical activity mediated the link between the personality facet of achievement and inflammation. Importantly, the study established some pathways for which personality affects disease: personality influences physical activity, which is an important marker for inflammation. Inflammation is related to disease. Personality traits, especially extraversion and conscientiousness, have been found to linked to immune functioning via inflammation (Mengelkoch et al., 2022). Neuroticism has been shown to have a larger effect on medication non-adherence than even low cognitive function (Jerant et al., 2011). Conscientiousness has a small, positive association with medication adherence (Molloy et al., 2014). As mentioned above, non-adherence is a risk factor for CVD for those taking cardiac medicine. Neuroticism and extraversion have both been associated with elevated levels of inflammation markers both concurrently and over time, suggesting that personality might influence CVD via inflammation (Armon et al., 2013).

Personality and psychopathology

Several models have been proposed to explain the relationship between personality and psychopathology (Klein et al., 2011; Sahoo et al., 2018; Widiger & Smith, 2008). In aetiological models, personality traits are proposed to have a causal effect on disorders. This effect can be direct: Neuroticism in particular has been shown to increase the risk of various anxiety and depressive disorders (Bienvenu et al., 2004; Jeronimus et al., 2016). The effect may also be indirect, neuroticism can represent a vulnerabil-

ity that moderates the effect of other events on the risk of developing a disorder. For instance, neuroticism may in combination with a stressful life event cause a major depressive episode. The effect can also happen in the opposite direction, with disorders causing a change in personality. An example of this is the scar hypothesis (Klein et al., 2011), in which the experience of going through a disorder lead to a permanent change in personality traits. In these aetiological models, personality may influence the risk of having a CVD indirectly via anxiety and depression.

In opposition to this, spectrum models assume that psychopathology and personality exists on a spectrum (Klein et al., 2011; Widiger & Smith, 2008). In this perspective, neuroticism can be a less severe form or a sub-type of anxiety. Hence, depression and anxiety can be considered as abnormal levels of normal personality traits, like negative affectivity or extraversion. Personality and psychopathology are caused by the same factors. Historically, Gray's 1970 behavioural inhibition and activation systems have been related to both neuroticism and extraversion as well as depressive and anxiety disorders (Kasch et al., 2002). Modern meta-analyses have also shown personality to be strongly associated with anxiety and depression, in particular neuroticism (Kotov et al., 2010).

From the perspective of the spectrum models, personality can influence CVD via the same pathways as depression and anxiety. Attempting to unify several of these personality-psychopathology models, Clark (2005) posited a hierarchical framework in which the three fundamental temperament dimensions of negative affectivity, positive affectivity and disinhibition caused the development of both personality traits and psychopathology. The tripartite model of anxiety and depression (Clark & Watson, 1991) can be placed within this framework. According to this model, anxiety and depression share the common symptom cluster of negative affectivity, which explains comorbidity between the disorders. Depression is uniquely characterised by low positive affectivity, which is not typical of anxiety. Due to the overlap of positive

and negative affectivity with personality, personality is able to explain anxiety and depression.

1.3 Antidepressants

The most common treatment option for depressive disorders is antidepressant medication (Vilhelmsson, 2013). Antidepressants are a diverse group of medications that can be roughly divided into different classes according to the manner in which each interacts with neurotransmitters. The first generation of antidepressants are called the tricyclic antidepressants (TCA). Adverse side-effects and dangers of misuse of the TCAs led to the development of second-generation antidepressants. The most well-known of these are the selective serotonin reuptake-inhibitors (SSRI). SSRIs increase the availability of serotonin outside the cells by blocking the reuptake of serotonin, prolonging the effects of serotonin (Harmer et al., 2017). They are the most commonly prescribed antidepressant (Cleare et al., 2015; Harmer et al., 2017). There are various side-effects of antidepressants, such as insomnia, sleepiness, dizziness, nausea, weight gain, mouth dryness and sweating (Bet et al., 2013). TCAs have more side effects than SSRIs and newer antidepressants. Other types of antidepressants include selective norepinephrine reuptake-inhibitors and atypical antidepressants. Though initially intended for treatment of depression, antidepressants are also used to treat other disorders like anxiety and pain management (Dharmshaktu et al., 2012; Offidani et al., 2013).

The development of antidepressants started when it was discovered that certain drugs administered to treat tuberculosis had an unintended antidepressant effect in patients (Lopez-Munoz & Alamo, 2009). This led to the monoamine hypothesis of depression, which states that depression is caused by deficient levels of monoamines like serotonin, norepinephrine and dopamine in the brain (Hirschfeld, 2000). The initial antidepressants were engineered to increase the availability of these monoamines

in the brain. A problem with the hypothesis is that the neurochemical changes following the application of antidepressants occurs within hours, while the therapeutic effects are only evident after several weeks of use (Harmer et al., 2017). One would expect the therapeutic effect to follow the neurochemical changes. Contemporary research has attempted to move away from a sole focus on purely neurotransmitter receptors to also consider intracellular signalling cascades, gene expression and protein translation.

1.3.1 Antidepressants and CVD

Antidepressants are an interesting factor in psychocardiology, because these medications can alternatively reduce or increase the CVD risk. Assuming that depression increases the risk of CVD, and that antidepressants reduce depression, the drugs would be expected to have beneficial effects on the risk of CVD. However, antidepressants have been found to be linked to increased risk of CVD (Jang et al., 2020). Particularly old TCAs are known to be cardio-toxic (Pacher & Kecskemeti, 2004). Antidepressants could affect CVD via indirect means: Common side-effects of antidepressants are sleepiness, sedation and subsequent physical inactivity (Bourin & Briley, 2004), which itself is a major risk factor of CVD (Visseren et al., 2021). This has led some researchers to investigate the cardiac risks associated with antidepressants. Several mechanisms for the link between antidepressants and CVD have been proposed (cf. Mathews et al., 2015). Depression increases inflammation and is linked to dysregulation of metabolism. SSRIs reduce the inflammation biomarkers that are increased by depression (Berk et al., 2013). Certain antidepressants have also been shown to reduce the platelet activation caused by depression down to normal levels (Seligman & Nemeroff, 2015).

Associations between antidepressants and CVD is a challenging topic to research, because large samples are needed to detect relatively rare occurrences of CVD in re-

lation to antidepressant use, and it is necessary to follow a sample for a length of time to properly ascertain exposure and endpoint. For this reason, many of the most impactful studies are based on large population databases that consolidate information about drug use and medical conditions from various registries. This has the drawback of using data post hoc for analyses it was not initially collected to test, and does not result in truly random sampling. This issue can be alleviated by using techniques like propensity score matching where each participant using antidepressants is matched with a non-user via certain risk profiles, with the goal of eliminating confounding due to differences between users and non-users (Austin, 2008). The use of registry data also does not allow for the case-control design of randomised controlled trials, limiting the ability to declare causality. Despite this, they are the best available sources of information at the moment, in addition to meta-analyses of randomised controlled trials.

Several large studies have been conducted on the association of antidepressants and CVD. A large study by Jang et al. (2020) of patients without CVD at baseline found that TCAs increased the risk of major adverse cardiovascular events in general, and strokes in particular. Noticeably, even a low dose of TCA was associated with an increased risk. Another large-scale study focusing on second generation antidepressants like SSRIs found that antidepressants were initially significantly related to increased risk of CHD, stroke, CVD death and all-cause mortality, in models that did not adjust for physical and mental health (Hansen et al., 2016). In the fully adjusted analyses, only the link with all-cause mortality remained significant. This indicated that the initially observed effects might be explained by other risk markers, including physical and mental health risk markers. A meta-analysis of 17 studies found that antidepressant use was linked to increased risk of mortality and new cardiovascular events in the general population (Maslej et al., 2017). When looking only at cardiovascular patients, however, antidepressants were not found to affect risk. A

meta-analysis found that antidepressants were linked to an increase in the risk of having an MI (Undela et al., 2015). TCAs were responsible for this increase, as there was no link between SSRIs and MI. A large cohort study of initially healthy participants found that the use of TCAs was associated with increased risk of CVD, but that found no effects of SSRI use (Hamer et al., 2011). A large-scale study of individuals diagnosed with depression found that antidepressants was mostly not associated with increased risks of CVD events, though there was some evidence that SSRIs were linked to decreased risk of MIs (Coupland et al., 2016). Another large study found that antidepressants, particularly SSRIs, reduced the odds of having an MI (Alqdwah-Fattouh et al., 2020).

These studies are not in agreement as to whether antidepressants are harmful, safe or even protective for CVD. In one of the most recent meta-analyses published, Tully et al. (2021) investigated the effects of psychological and pharmacological interventions in patients with coronary artery disease. The authors concluded that there exists evidence that psychological may result in reductions in depression, but that these findings were of low certainty due to bias and lack of trials. There was more certainty in the findings that pharmacological interventions (mainly antidepressants) reduced depression. The authors found no beneficial effects of pharmacological interventions on mortality or cardiac events, but this might have been due to a lack of published findings. Current guidelines recommend SSRIs as a first-line treatment for patients with underlying CHD (Cleare et al., 2015).

1.4 Gender and sex differences in psychocardiology

Differences between men and women are referred to as sex differences or gender differences; these terms are sometimes used interchangeably. Sex refers to biological characteristics and are determined by hormones and chromosomes (Connelly et al., 2021). Gender, on the other hand, refers to a partially self-determined identity

shaped by cultural, societal, behavioural and psychological factors. It is possible that a person's sex and gender do not match up, for instance in the case of transgender or gender-neutral individuals. In the field of psychocardiology, studies usually focus on either sex or gender, or else they are unclear as to which of the two they refer to. Few studies, if any, explicitly focus on individuals who fall outside the traditional categories of male and female. This may be warranted, since transgender individuals have higher prevalence of anxiety and depression compared to cisgender (those whose gender identify matches the sex assigned at birth) individuals (Chumakov et al., 2021).

Sex and gender can influence cardiac risk factors in similar ways, via different mechanisms. For instance, from the age of adolescence men have a higher blood pressure than women (Dasgupta et al., 2006). The difference is thought to be caused by sex hormones. However, certain societal factors that disproportionately affect women, like educational inequalities, has been shown to increase blood pressure in women (Neufcourt et al., 2020).

Women typically develop CVD later in life than men (Worrall-Carter et al., 2011) Initially, women were marginalised in the research of CVD (Feldman, 2020). Subjects in studies were male, and there was a belief that oestrogen protected women from CVD. Their cardiac symptomatology differs from that of men: Women are less likely to have traditional symptoms of CHD, like chest pain (Canto et al., 2012). They are more likely to have non-specific symptoms, like fatigue, sleep disturbances, mild discomfort without chest pain, and to have milder symptoms in general (Keteepe-Arachi & Sharma, 2017). They are also more likely to present with non-ST-elevation MI instead of ST-elevation MI like men (Mehta et al., 2016). Hence, women are more at risk of being misdiagnosed, or having undetected CVD (Keteepe-Arachi & Sharma, 2017).

Women are more at risk of depression and anxiety than men are (Seedat et al.,

2009). If depression and anxiety affect CVD risk, one could expect that this association was different for the two genders. Women tend to report more somatic symptoms than men (LeGates et al., 2019). There are also stable differences in the mean level of personality traits among men and women: women tend score higher on neuroticism, agreeableness and certain facets of extraversion and openness to experience (Schmitt et al., 2017). If there are effects of anxiety, depression or personality on CVD risk, then this is another arena in which gender could affect CVD risk.

Traditional CVD risk factors have different potency, significance and prevalence for men and women (Connelly et al., 2021; Gao et al., 2019; Mauvais-Jarvis et al., 2020). For instance, age has been found to be a stronger risk factor for men (Gao et al., 2019). Traditional cardiovascular risk scores, like the Framingham Risk Score (D'Agostino et al., 2008) tend to underestimate the risk for women (Lakoski et al., 2007; Thurston et al., 2013). This is a reason to focus on generating more knowledge about novel risk markers, as they might increase the precision of future risk scores for women.

While there is no clear consensus as to whether sex differences in antidepressant efficacy exists, there is evidence that men respond better to TCAs while women respond better to SSRIs (LeGates et al., 2019). Female sex hormones are implicated in this observed difference: as women reach menopause the efficacy of SSRIs decrease, but this decrease can be attenuated by hormone replacement therapy (Thase et al., 2005). Another potential explanation for a sex difference in antidepressant efficacy is that men and women are predisposed to different subtypes of depression, with women reporting more somatic symptoms and more atypical depression than men (LeGates et al., 2019).

1.5 Challenges and gaps in the field

Whether anxiety is a risk factor for CVD is not yet established to the same degree as it is for depression. While some studies have concluded that it is (Batelaan et al., 2016; Tully et al., 2016), some studies have found that the initially significant effect of anxiety disappeared after adjusting for depression (cf. Miloyan et al., 2016). Hence, co-morbidity with depression is a methodological consideration that has be taken into account in future studies on anxiety and CVD.

There is scarce research on personality as it relates to CVD, if disregarding the studies done on the controversial types A and D personality. It is, however, well-documented that certain personality traits increase the risk of mental disorders, like depression and anxiety (Lahey, 2009; Ormel et al., 2013). This has not been adequately reflected in psychocardiology research yet. There is a need for studies that examine the effects of personality traits on CVD risk.

Personality affects many aspects of a person's behaviours and thoughts. In the spectrum model of personality and mental disorder, personality traits represent the non-pathological ends of a continuum with mental disorders at the opposite end. In this view, the associations of depression or anxiety with CVD could be reflective of a dispositional tendency towards, for instance, negative affectivity, and that this is the true cause of increased CVD risk. This would line up with the studies mentioned above that find that negative affectivity is part of type D personality that is central to the development of CVD.

Neuroticism in particular has received much attention for its role in general health outcomes (Lahey, 2009) and common mental disorders (Kotov et al., 2010). It partially overlaps with symptoms of mental disorders and share genetic and environmental determinants with mental disorders (Ormel et al., 2013). Recent studies have addressed the importance of incorporating neuroticism when studying mental health

and CVD (Li et al., 2021).

A challenge in the field is the heterogeneity in terms of instruments, terms and operationalisations being used in the various studies. Some studies examine CVD, others CHD and still others MI. While it is possible that there is a central factor common to all three, it is also possible that some relationships are specific to only MI or the broader CHD due to the nature of these disorders. A link between anxiety and MI does not demonstrate that all CVDs are related to anxiety, for instance. Studying CVD in terms of its sub-classifications allows for more nuanced and specific knowledge. Similarly, various instruments and methods have been used to measure anxiety and depression. They have also been operationalised invariable as dichotomous categories, polytomous categories and continuous dimensions. Different operationalisations have implications for interpretation and applicability of studies. Dichotomising continuous variables, while helpful in clinical practice and predictions, is discouraged in aetiological research as it reduces the statistical power of analyses (Altman & Royston, 2006). This may result in under-powered studies, which are a serious issue in quantitative research fields (Ioannidis, 2005).

The study of CVD occurring in initially healthy samples requires large samples to ensure enough cases are detected. This is one of the reasons many studies utilise registry data, or data collected for other study purposes. Often these studies will focus on a specific group: individuals from one country, individuals of one gender, individuals with certain conditions. Valuable information can be gleaned from these studies, but care must be shown when generalising to other populations. Certain populations are also at increased risk of CVD, like the elderly and those with diabetes (Piepoli et al., 2020). Studies of these populations are important since they benefit those at risk, but again, generalisation must be carefully considered.

As was previously asserted, the cardiovascular safety of antidepressant use is not firmly established. Findings from several large studies run partially counter to each

other but may imply that TCAs are more likely than SSRIs to increase CVD risk. This is expected from the existing knowledge of TCAs. Given that depression and CVD are among the most common diseases in the world, and that depression increases CVD risk, it is important to know whether antidepressants, which are a common treatment option for depression, affect CVD risk.

There are gender and sex differences in prevalence and presentation of depression, anxiety and CVD. Researchers have also established potential differences concerning antidepressants, and personality traits are differently distributed among men and women. For this reason, gender-specific risk profiles of CVD for men and women are warranted. It has still not been unequivocally established that there are sex or gender differences in the efficacy of antidepressants, for instance (LeGates et al., 2019).

1.6 Aims and Objectives

The general aim of this thesis is to investigate some of the lingering questions in the field of psychocardiology due to the current lack of knowledge about the effects of psychological variables on CVD risk (Levine et al., 2021). First, depression can be considered an independent risk factor for CVD, and anxiety has also been shown to be a CVD risk marker, yet it is unclear if the effect of anxiety is independent of depression. Secondly, it is possible that the observed effects of anxiety and depression on CVD risk are caused by underlying dispositional factors such as personality. Finally, clarifying the impact of antidepressant use on cardiovascular risk and whether this effect is sex-specific would benefit men and women alike.

1.6.1 Paper I

The aim of the study was to investigate whether anxiety increased the risk of CVD in elderly men when analyses controlled for depression. Recent studies have found anxiety to be a risk factor for depression, but a weakness in these studies is that

they rarely adjusted for the effect of depression. Since different CVD endpoint have yielded unique results, we analysed CHD and CER separately. We dealt with previous history of CVD by running to sets of analyses. In the first, previous history of CVD was adjusted for in the statistical models. In the second, we split the sample into a group with *no* prior history and a group *with* prior history of CVD and analysed both groups. Thus, our research questions were:

- Will depression increase the risk of both CHD and CER?
- Will the effects of depression be consistent across the subgroups of participants with and without a history of CVD?
- Will anxiety increase the risk of CHD or CER when adjusting for the effects of depression?

1.6.2 Paper II

The aim of this study was to review the recent literature on anxiety and CVD. The last decade had seen several meta-analyses and reviews of the cardiac consequences of depression, but less so for anxiety. The paper started by summarising the existing meta-analyses on anxiety and CVD. A major limitation of many studies on this topic is the failure to control for the effect of depression. Then we searched for studies published in 2009 or later, that investigated the effects of anxiety on CVD endpoints. Of these, we only included those that controlled for the effects of depression in the analyses.

1.6.3 Paper III

The aim of this study was to investigate the associations of antidepressant use and MI. Antidepressants are a common treatment option for individuals suffering from depression. There are lingering questions about the effects of antidepressant treatment

on the risk of developing heart disease. There are also well-documented reasons for why effects of antidepressants could be sex-specific (LeGates et al., 2019). Thus, an investigation into the cardiovascular effects of antidepressants should examine men and women separately. This paper had the following research questions:

- Is there an association between antidepressant use and MI?
- Is this proposed association sex-specific?

1.6.4 Paper IV

The aim of this study was to contribute to the study of psychological risk profiles of CVD for men and women. We explored the role of the personality traits neuroticism and extraversion in CVD. To examine whether anxiety and depression's status as risk markers of CVD were independent of dispositional factors like personality. As previous studies have established unique effects for the different categories of CVD, two types of CVD outcomes were examined: MI and stroke. We investigated the associations of the psychological variables on the two CVD outcomes for men and women separately. The paper had the following research questions:

- Are neuroticism or extraversion associated with MI or stroke?
- Are these proposed associations sex-specific?

2. Methods

The papers in this thesis are based on two health registries (DÅR and NorPD), a population cohort measured at two time points (The HUNT Study), and a longitudinal sample (MrOS), as well as a literature review. In the following section, the contents of these information sources are explained, as well as the instruments used in the papers, the analyses used, and the search strategy used for the literature review.

2.1 Samples and procedures

2.1.1 Paper I: MrOS

The Osteoporotic Fractures in Men (MrOS) Study was a longitudinal research study funded by the National Institutes of Health in the U.S. (Blank et al., 2005; Orwoll et al., 2005). Initially, 5994 elderly men from Birmingham, Alabama; Minneapolis, Minnesota; Palo Alto and San Diego, California; Pittsburgh, Pennsylvania and Portland, Oregon were recruited for the study. Various examinations were performed, and the men were followed for a period of several years with repeated visits. In a subsection of the study, the MrOS Sleep Study, cardiovascular events were recorded (Mehra et al., 2007). Data from this subsection was used in Paper I.

Of the original sample, 3135 participants were assessed in the period between

December 2003 to March 2005 and included in the MrOS Sleep Study. This was the baseline, and participants were then followed until February 28, 2015. During this follow-up period, participants were contacted every four months and asked about any hospitalisations or treatment for CVD-related conditions. Indications of CVD events were compared against medical records. The men who were recruited for the study were community dwellers above the age of 66. They completed self-administered and interviewer-administered questionnaires and underwent clinical examinations.

2.1.2 Paper II: Literature review

Paper II was a narrative literature review. We searched the online databases MEDLINE, Psycinfo, Global Health and Google Scholar using the keywords: "anxiety OR anxiety disorder OR generalised anxiety disorder OR panic OR panic disorder AND cardiovascular disease OR heart disease OR heart attack OR myocardial infarction OR stroke". Only papers that included depression in the statistical models were included. We also focused on longitudinal studies that had been published after 2008. We identified six meta-analyses and fifteen single, longitudinal studies.

2.1.3 Paper III: HUNT

Data from the Trøndelag Health Study (HUNT, formerly known as the Nord-Trøndelag[1] Health Study) was used for this paper. The HUNT Study is a collaboration between HUNT Research Centre (Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology), Trøndelag County Council, Central Norway Regional Health Authority, and the Norwegian Institute of Public Health. It is a large health study that started in 1984 (Krokstad et al., 2013). It collects data from the population in the area of Nord-Trøndelag in central Norway. This has been done four

[1]The counties of Nord-Trøndelag and Sør-Trøndelag merged in 2018, after being separated for 214 years. The current county that encompasses the former county of Nord-Trøndelag is called Trøndelag. Since the merger happened after the data collection, and the term is still a valid name for the geographical area the former county occupied, Nord-Trøndelag is still used in this text.

times since the conception of the HUNT Study. By using the Norwegian national identity number, which is a unique identifier issued to each person born or settled in Norway, participants could be followed longitudinally and linked to other health registries. Data from the second and third wave (HUNT2 and HUNT3) was used in this paper. The HUNT2 Survey was carried out in 1995–1997, while the HUNT3 Survey was carried out in 2006–2008. In Paper III, data from the Norwegian Cause of Death Registry (DÅR) and the Norwegian Prescription Database (NorPD) was used.

The study included a total of 31 765 participants whose mean age when data collection began was 50.36 years (SD = 17.51). Of these, 14 875 (46.83%) were male. Participants were followed from the start of the HUNT2 Survey and until the end of the HUNT3 Survey. For those that did not participate at HUNT3, the follow-up ended on the 31st of December, 2008. To be included in the study sample, participants must have participated at HUNT2 and also either 1) participated at HUNT3 or 2) died from MI during the follow-up. Drop-out analyses have been performed by Langhammer et al. (2012), investigating those that dropped out of the cohort in HUNT3. Among their findings was that drop-outs were more likely to be suffering from diseases like CVD.

2.1.4 Paper IV: HUNT

Paper IV also used data from the HUNT Study, but only from the HUNT3 Survey. It also used data from DÅR to give information about which participants had fatal MI or stroke after the end of the HUNT3 Survey. Data from the DÅR was available from the time of HUNT3 and until the end of 2017. Thus, the time period from the start of the HUNT3 Survey to 31st of December 2017 was the follow-up period. The average follow-up time was 10.38 years, during which the date of fatal MI or stroke was recorded. A total of 32 383 participants were included in the sample. The average age at the start of the HUNT3 Survey was 52.25 (= 14.18). Of these, 18 490 (57.10%) were women.

2.2 Instruments

The following details the instruments, measurements and variables recorded in Papers I, III and IV.

2.2.1 Paper I

CVD

Participants self-reported any history of CVD at the start of the MrOS Study. Additionally, they were followed up after the ancillary sleep study. During this time, they were contacted every four months and queried whether they had experienced any new cardiovascular events. When participants reported a CVD event, their medical records were obtained and adjudicated by trained cardiologists. In the case of fatal events, hospital records were also obtained. The follow-up period lasted for 13–15 years, and the average time to a CHD event was 8.0 years (SD = 3.4), while the average time to a CER event was 8.5 years (SD = 3.0). In this study, CHD included any of the following events: acute myocardial infarction, ischemic congestive heart failure, coronary bypass surgery, mechanical coronary revascularisation, ST and non-ST elevation MI, hospitalisation because of unstable angina, sudden CHD death or other recorded CHD events. CER events included stroke and transient ischemic attacks. Anxiety and depression were measured during the sleep visit.

Anxiety and depression

Anxiety and depression were measured using the Goldberg Anxiety and Depression Scales (GADS, D. Goldberg et al., 1988). Each condition was assessed using a 9-item scale, on which the participants indicated the degree to which they had experienced symptoms during the last four weeks. Examples of items include: "Have you felt keyed up, on edge?", "Have you been worrying a lot?" (anxiety), "Have you had low

energy?" and "Have you had loss of interests?" (depression). A composite score was calculated from these items, and this score was then dichotomised in the following manner: Depression scores higher than 2 and anxiety scores higher than 5 indicated that the participant had a 50 percent chance of having a clinically significant disturbance.

It should be noted that there is scant evidence on the validity of the GADS. Koloski et al. (2008) found the GADS to be an acceptable measure in a sample of elderly women, but recommended it be used as a unitary construct instead of as two separate scales. While studies have raised questions about the validity of the GADS (Koloski et al., 2008; Therrien & Hunsley, 2012), others have found support for the use of GADS in the originally intended format with two separate scales for anxiety and depression (Kiely & Butterworth, 2015; Mackinnon et al., 1994).

Covariates

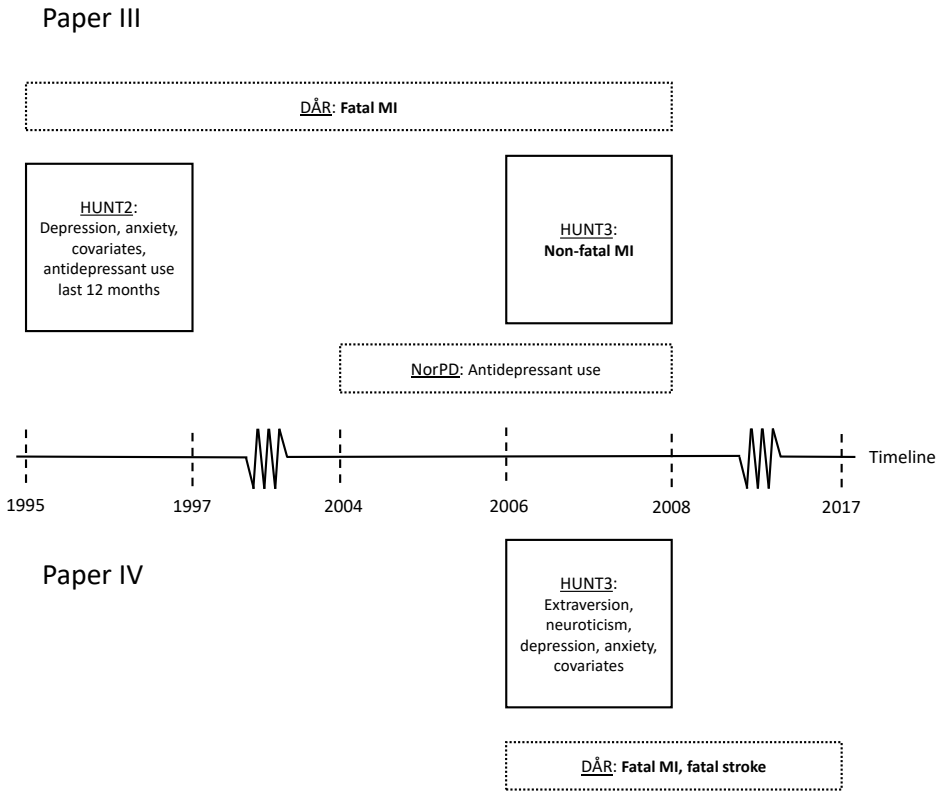
Physical activity was measured using the Physical Activity Scale for the Elderly (Washburn et al., 1993). Sleep quality was measured using the Pittsburgh Sleep Quality Index (Buysse et al., 1989). Body mass index was calculated based on the height and weight of participants at the sleep visit. Cholesterol was measured using serum samples to detect oxidised low-density lipoprotein (Harrison, 2014). Blood pressure was measured using a mercury sphygmomanometer. Weekly alcohol consumption, diabetes, smoking status, ethnic group, age and the use of antidepressants were measured using self-reports.

2.2.2 Papers III and IV

Papers III and IV both used data from the HUNT3 Survey and the DÅR. Paper III additionally used data from the HUNT2 Survey and NorPD. Because both papers implemented the many of the same instruments and measurements, they are presented

jointly. Further information on the design of the HUNT Study can be found in Holmen et al. (2003), Krokstad et al. (2013), and Langhammer et al. (2012). A graphical presentation of when the various variables were measured for the two papers is presented in Figure 2.1.

Figure 2.1: Timeline of measurement of variables for Papers III and IV.



Note. MI = myocardial infarction. DÅR: Norwegian Cause of Death Registry. HUNT = Trøndelag Health Study. NorPD = Norwegian Prescription Database. Underlined names indicate source of data, **bolded variables** indicate outcomes. Dotted boxes indicate registry data collected continuously during the time period, lined boxes indicate HUNT data sampled once for each participant during the time period.

CVD

In the HUNT2 and HUNT3 Surveys, participants were interviewed by staff at the HUNT Research Centre and asked whether they currently have or have previously

suffered from any of the following: MI, angina pectoris, stroke. Additionally, the DÅR was used to identify those who had died from MI or stroke during the study periods of Papers III and IV. This was based on the cause of death registered on the report of death that is produced for any person dying in Norway. The cause of death was specified using the World Health Organisation's International Statistical Classification of Diseases and Related Health Problems (ICD). The ICD is regularly updated, and the current version is the ICD-10. The change from ICD-9 to ICD-10 happened around the same time as the HUNT2 Survey. Thus, some of the deaths in the study time of Paper III was recorded with the ICD-9. For most of the deaths associated with Paper III and all of the deaths in Paper IV, ICD-10 codes were used. ICD-10 codes I21 to I22 and ICD-9 code 410 indicated death by MI, while ICD-10 codes I60 to I69 indicated death by stroke. Anyone that reported having an MI between the HUNT2 and HUNT3 Surveys, or that was registered as dying because of MI in the same time period, was considered as having MI in Paper III. In Paper IV, only those who died from MI or stroke *after* the HUNT3 Survey were considered as having MI or stroke.

Anxiety and depression

Anxiety and depression were measured with the Hospital Anxiety and Depression Scales (HADS) at both the HUNT2 (Paper III) and HUNT3 (Paper IV) Surveys. It was originally developed to measure anxiety and depression in outpatients in a hospital setting (Zigmond & Snaith, 1983). It was intended as a self-assessment tool for screening. HADS consists of 14 items, 7 which measure anxiety and 7 which measure depression. Each item consists of a statement, like "I can sit at ease and feel relaxed", "I get a sort of frightened feeling as if something awful is about to happen" (anxiety), "I feel as if I am slowed down", "I can laugh and see the funny side of things" (depression). Certain items are reversed. Test-takers are instructed to consider

each item in terms of how they felt during the last week, and then give them a score ranging from 0–3, where 0 indicates disagreement and 3 indicates agreement. From the individual items a sum score is produced for each sub-scale, with each sub-scale having a maximum score of 21. The original study included cut-off scores indicating the likelihood of a disorder: 8–10 were doubtful cases, 11 or more were definitive cases.

While the HADS was intended for outpatients in a hospital setting, later studies validated it for use in other populations as well (Bjelland et al., 2002). Since it was intended for outpatients at a hospital, the HADS does not measure somatic symptoms (fatigue, insomnia), as this would have overlapped with other conditions that patients were seeking care for (Snaith, 2003; Zigmond & Snaith, 1983). HADS has also received some criticism. A systematic review of 50 studies found that, although half of them replicated a two-factor structure, the latent structure of the instrument was uncertain (Cosco et al., 2012). They suggested HADS instead be used as a unidimensional measure of general distress. A meta-confirmatory analysis found that the best latent structure for HADS was a two-factor model with an additional general distress factor (Norton et al., 2013), supporting HADS as measuring general distress. Studies of HADS as a two-factor model has found the depression factor to reflect anhedonic depression (Langvik et al., 2016) Despite its shortcomings, the HADS has been used extensively since it was first published. Other studies have found support for the two-factor structure of the HADS (Djukanovic et al., 2017).

In Papers III and IV, a Norwegian translation of HADS was used. This translation was developed by the HUNT Study (HUNT, 2021), and has shown good validity (Mykletun et al., 2001). In line with recent usage of the HADS (cf. Burns et al., 2014), it was used as a continuous measure of distress level of depression and anxiety.

Personality

The personality traits neuroticism and extraversion were measured at the HUNT3 Survey using a subset of items from the Eysenck Personality Questionnaire (EPQ, H. J. Eysenck & Eysenck, 1975). The EPQ is based on Eysenck's biological theory of personality which assumes that the personality traits are grounded in specific physiological systems (Corr, 2004). Six items from each of the two personality scales from the Norwegian version were used in the HUNT Study (S. B. G. Eysenck & Tambs, 1990). Respondents were instructed to consider themselves as they normally are, and then presented with each item which contained a statement. All items started with "Do you consider yourself ...". Examples of extraversion items: "A life of the party type person?" and "Do you like meeting new people?". Examples of neuroticism items: "Are you often worried?" and "Do you often feel that you lose interest?". Possible responses were yes or no. The dichotomous scoring format of the EPQ has been criticised for being inferior to more continuous grading schemes (Muñiz et al., 2005). A comparison to the Myers-Briggs Type Indicator and Adjective Check List found favourable validity for the neuroticism and extraversion scales of the EPQ (Wakefield et al., 1976). A study of 34 countries found that the personality traits of the EPQ were strongly replicable in all countries (Barrett et al., 1998). A review of 44 studies found that the extraversion and neuroticism scales of the EPQ had adequate reliability values (Caruso et al., 2001). It was found to be a valid measure of personality across 33 different cultures (Bowden et al., 2016).

Antidepressant use

The use of antidepressant medication was ascertained via the use of data from the NorPD, as well as self-reports from the HUNT2 Survey. At HUNT2, participants were asked whether they had used antidepressants during the last 12 months. Every prescription written for a participant from 2004 and onwards is recorded in the

NorPD. From this we created a composite measure which recorded whether participants had received any prescriptions for antidepressant medication in the time between the before HUNT2 and between 2004 and 2008 (the end of the HUNT3 Survey). If a participant only used antidepressants during the time window between the end of the HUNT2 Survey and the start of the NorPD in 2004, they would not be included in this measure of antidepressant use. Medication use was logged according to the Anatomical Therapeutic Chemical system. The following codes were used: N06AA (TCA), N06AB (SSRI), N06AF (Monoamine oxidase inhibitors, non-selective), N06AG (Monoamine oxidase A inhibitors) and N06AX (Other antidepressants). To be able to run separate analyses for each type of antidepressant, the participants were divided into the following groups: TCA, SSRI and other antidepressants. The latter category included any users of monoamine oxidase A inhibitors and other antidepressants — there were no users of non-selective monoamine oxidase inhibitors in the sample. Membership in a group was not independent, a participant could belong to more than one group if they had used more than one type of antidepressants.

Covariates

Systolic blood pressure was measured by nurses using oscillometry. The mean value of the second and third of three measurements were used. The participants were seated for two minutes before the measurements were taken. Waist-hip ratio was measured at the widest part of the hip and at the level of the umbilicus for the waist. Cholesterol was measured via enzymatic cholesterol esterase methodology. Age, smoking status and the presence of diabetes were measured using self-reports on questionnaires. Sex was based on the records linked to the Norwegian National Identity Number, and thus records the sex of a person at birth. In Paper III these measured were from the HUNT2 Survey, while in Paper IV they were from the HUNT3

Survey.

2.2.3 Operationalisation

Whether to operationalise depression and anxiety as continuous measures or as categories has theoretical and statistical implications. Researchers have found that the choice of categorical or continuous operationalisations of variables affects the results of their research. In a sample of acute coronary syndrome patients, Sanchez et al. (2021) found different patterns of significant effects when analysing depression measured by the Beck Depression Inventory as continuous or categorical. Bjelland et al. (2009) used categorical and continuous anxiety and depression, measured with the HADS, and found that the continuous measures had better predictive power. Researchers have found that even subclinical levels of anxiety increase the risk of heart disease (Rozanski et al., 1999). As the cost of dichotomising continuous variables is considerable (Altman & Royston, 2006), and based on recommendations (Bjelland et al., 2009), continuous measures of anxiety and depression are used in Papers III and IV.

Several of the variables included in the papers of this thesis are based on self-reports. This includes diabetes, CVD variables, anxiety, depression and personality. Self-reports are sometimes considered to be less objective than patient records or health registry data (St. Clair et al., 2017). Ideally, studies would compare patient records with self-reported diseases, but this is not always feasible. Studies on the HUNT Surveys have shown high overlap between self-reports and patient records on diabetes, indicating that participants accurately report their health status (Midthjell et al., 1992). Using self-report on instruments is a valid method of identifying diseases (Skinner et al., 2005).

2.3 Analyses

The following is a description of the statistical analyses that were performed in Papers I, III and IV.

2.3.1 Paper I

We investigated whether anxiety and depression affected the risk of having a CHD or a CER event. Cox proportional hazards models were used to investigate this. Anxiety and depression were entered into models separately, together, and including covariates. Analyses run on the total sample included previous history of CVD as a covariate. Separate analyses were run on those with prior history of CVD and those without previous CVD events. Forty participants were dropped because they had missing data on variables used in the analyses.

2.3.2 Paper III

We investigated whether antidepressant use affected the odds of having MI. Logistic regression models were calculated. Several models were run: initially, the simple effects of antidepressant use and depression were investigated, then models including both these variables. Lastly, anxiety and other covariates were added to the model. In addition to running these models on the total sample, separate models were also run for men and women. Participants that reported MI or angina prior to the start of the follow-up were excluded. Those who were considered to have had an MI event were those who reported MI during the follow-up, or who died from an MI during follow-up. The follow-up period lasted from the start of the HUNT2 Survey in 1995 to the end of 2008. Follow-up analyses were performed to investigate whether the different antidepressant classes of TCAs, SSRIs and other antidepressants had differing effects on MI risk, and whether the antidepressant users differed significantly from the non-

users on the predictor variables.

2.3.3 Paper IV

Cox proportional hazards regression was performed on the data. The risk of death from MI and stroke from anxiety, depression, neuroticism and extraversion was investigated separately. Initially, simple effects of each predictor were examined. Then subsequent models included more of the variables, terminating in a full model with all predictors and covariates. Analyses were run using both the whole sample and men and women separately.

2.4 Ethical considerations

Paper I was based on the MrOS Study. In the MrOS Study, ethics approval was secured at each of the sampling sites across the U.S. Additionally, written, informed consent was obtained from all the participants.

Paper III and IV used data from the HUNT Study, as well as the DÅR and NorPD. The HUNT Study was given a licence to collect data (konsesjon HUNT1,2,3 og UngHUNT3 15/01521-11/GRA). The Regional Committee for Research Ethics (REK) approved the ethical aspects of the HUNT2 Survey (REK reference number 152/95/AH/JGE) and the HUNT3 Survey (REK reference number 4.2006.250). Participants in the HUNT Survey were informed that their responses could be used in research, and that data from national registries could be combined with their HUNT data. In order for this merging of data to happen, the HUNT Study needed to store each participant's unique Norwegian national identity number, as this is the only way to match participants across registries. These identity numbers were only handled by independent third parties, and never by any of the researchers involved in any of the papers. The third parties in this case were the DÅR and the NorPD. They merged the data files and deleted the identifying national identity numbers before giving the data

files to the researchers.

Both the DÅR and the NorPD registries are within the jurisdiction of the Norwegian Institute of Public Health. The DÅR is a national health registry with valid licences to store and obtain data about the citizens and inhabitants (at time of death) of Norway. A research project that applies for data from the DÅR or NorPD to link it with other registries is required to get approval from an independent ethics committee. The linkage that was done for Papers III and IV, in which data from the DÅR, the NorPD and the HUNT2 and HUNT3 Surveys was approved by the REK (REK reference number 2018/619). The HUNT Research Centre approved the use of data from the HUNT2 and HUNT3 Surveys (HUNT reference number 2018/13248/TRS). A detailed Data Protection Impact Assessment was also created to ensure that the project's handling and storage of data was performed in a secure manner related to the EU's General Data Protection Regulation. The Norwegian Institute of Public Health approved the use of data from NorPD and DÅR, and linkage with the HUNT Study (project number PDB 2517, case number 18/11182).

3. Results

3.1 Paper I

Paper I investigated the roles of anxiety and depression in having a CHD or CER event respectively. To examine this, we calculated cox regression models with mortality or morbidity from CHD and CER events separately.

The sample consisted of 3095 elderly men, with the mean age at baseline being 76.38 (SD = 5.54) years old. By the end of the follow-up period, 612 participants had experienced one or more CHD events, while 291 had experienced one or more CER events. Almost nine percent of the participants had anxiety scores above 5, indicating a 50 percent chance of having a clinically significant disturbance. Almost thirty-two percent of the sample had a depression score above 2, indicating the same. A large portion of the sample had a previous diagnosis of CVD before the start of the study (38.61%). Those who experienced a CHD or CER event during the study more often had a previous diagnosis of CVD than those with did not have a CHD or CER event.

When analysing the total sample, anxiety had an initial significant association with CHD (HR = 1.41). This HR decreased and became non-significant (HR = 1.06) after adjusting for depression, which had a significant association with CHD (HR = 1.68). In the final model, adjusting for all covariates, anxiety showed no impact on

CHD, while depression had a slightly attenuated, but still significant impact on CHD.

Subsequent analyses focused on sub-samples that had either a) experienced no CVD event prior to the study, or b) had a prior history of CVD. In neither of these sets of analyses were anxiety significantly related to CHD or CER. Depression, however, was associated with increased risk of CHD events in the sub-sample with a history of CVD. The same relationship was observed initially for participants with no history of CVD, but it became non-significant when adjusting for covariates.

Throughout all the analyses with CER as the outcome, neither anxiety nor depression was significantly related to a change in risk. Only previous history of CVD was significantly associated with CER risk.

3.2 Paper II

In this narrative review, the results took the form of a summary of the six meta-analyses and fifteen recent large-scale single studies that addressed the role of anxiety in CVD genesis. Of the single studies, only those that adjusted for the effect of depression were included in the review.

The meta-analyses were published between 2010 and 2017, and included between 8 and 46 studies. Of the meta-analyses, most found that anxiety increased the risk of CHD, MI, cardiovascular mortality, stroke and heart failure. However, only two of them included adjustments for depression in their analyses of anxiety (Batelaan et al., 2016; Tully et al., 2015). They found no difference among the group of studies that did and did not adjust for depression: anxiety (panic disorder in the study by Tully and colleagues) was still significantly related to CVD outcomes after adjustment.

There was a large amount of heterogeneity in the results of the studies included in the review. Some found an association between anxiety and some form of CVD even when adjusting for depression, while others did not. There are numerous potential reasons for this. Cardiovascular disease was variously studied as CVD in general,

sub-classes of CVD like MI, stroke, CHD or heart failure. Some distinguished between cardiac mortality and morbidity, some combined these endpoints. This made it harder to determine whether anxiety was related to CVD in general or to specific forms of CVD. Some of the studies followed healthy populations, while others studied groups suffering from other diseases like diabetes. Other studies followed a specific group, like elderly men. This would make it more tenuous to generalise to a general population. A few studies suggested that anxiety had a beneficial cardiac effect, by reducing CVD risk.

3.3 Paper III

Logistic regression models were calculated to investigate the associations of antidepressant use, depression and risk of MI. Initially, the whole sample was analysed, then separate models were calculated for men and women to investigate sex differences.

Of the total sample, 4055 had used antidepressants, 404 had a fatal MI and 649 had a non-fatal MI, while 6 individuals had both non-fatal and fatal MI. More women than men had used antidepressants, and more men than women had MI. The results of analyses on the total sample showed that antidepressant use was associated with a decrease in the risk of having an MI (OR = 0.49), even when adjusting for all covariates. In these fully adjusted models, depression was associated with a marginal increase in the risk of MI (OR = 1.03), while anxiety was not related to MI.

In sex-specific, fully adjusted analyses, the decrease in MI risk for antidepressant users seemed stronger for women (OR = 0.46) than for men (OR = 0.53). However, when an interaction term between antidepressant use and sex was added to the analyses of the total sample, it was not significant. This indicated the absence of sex-specific effects of antidepressant use on MI risk.

Follow-up analyses were performed by running the same fully adjusted analyses in participants grouped by what type of antidepressant medication they used: TCA,

SSRI or other antidepressants. These groups partially overlapped, since some participants had used more than one type of antidepressant and thus appeared in more than one group. The results indicated that both TCAs and SSRIs were associated with a decreased risk of MI in the total sample as well as for both men and women. There were no significant associations of other antidepressants in any condition.

Additional follow-up analyses examined whether the participants that used antidepressants differed from the non-users on the variables that were included in the previous analyses. The antidepressant users had significantly higher scores on anxiety ($d = -0.67$) and depression ($d = -0.47$), they had smoked for longer ($d = -0.22$) and a higher proportion of them were female ($\phi = 0.12$).

3.4 Paper IV

Cox proportional hazards models were calculated separately for the two outcomes of MI mortality and stroke mortality. Additionally, separate models were run for men and women, in addition to a model for the total sample. On average, the time from the entry into the study to an endpoint (mortality or censoring) was 10.48 years. During this time, 142 participants had died of MI and 111 participants had died of stroke.

In the fully adjusted models, neuroticism (HR = 1.23) and depression (HR = 1.07) significantly increased the risk of MI in the total sample. These effects disappeared when analysing only women. For men, only neuroticism (HR = 1.26) was associated with the risk of having an MI. None of the psychological variables were significantly associated with the risk of stroke in the total sample when adjusting for all covariates. The same was true for men. For women, however, extraversion (HR = 1.21) was associated with a significant increase in the risk of stroke in the fully adjusted models.

In the fully adjusted models, anxiety did not have any significant associations with MI or stroke, despite being significantly related to MI in previous models without all covariates. Depression was only related to MI (HR = 1.07), and only in the

total sample. Neuroticism and extraversion showed more consistent patterns of association with MI and stroke than anxiety and depression, as they more often emerged as significant predictors in the final models.

4. Discussion

4.1 Anxiety as risk marker

In Paper I, we failed to find evidence linking anxiety to changes in the risk of developing CHD or CER when adjusting for the effects of depression. This indicates that anxiety does not have an independent effect on CHD or CER. Despite the many studies that have found a link between anxiety and CVD (cf. Emdin et al., 2016; Roest et al., 2010), researchers have pointed out the need to adjust for confounding by depression (Batelaan et al., 2016). A potential limitation of Paper I was that its sample only included men, and that the men were above the age of 67. However, in terms of real-world utility, these are among the most likely to develop CVD, and as such, they are of specific interest to researchers seeking to reduce preventable CVD cases.

Papers III and IV, which studied different populations and samples, corroborated the findings from Paper I. In neither of these studies was anxiety linked to changes in risk of CVD when adjusting for depression. In Paper III, anxiety was initially found to be associated with a decreased risk of MI, but this association disappeared after model adjustment, supporting the notion that comorbid depression can explain previously established links between anxiety and CVD. Even though the intuitive conclusion that can be drawn from Papers I, III and IV is that anxiety is not an independent CVD

risk marker, the research cited in Paper II invites caution about this conclusion. The recent meta-analyses generally agreed that anxiety was related to CVD, and two of them demonstrated this to be true even when adjusting for depression.

The HADS was used to measure anxiety and depression in Papers III and IV. Some researchers have suggested that the HADS is better used as a measure of general distress instead of as measuring two separate constructs (Cosco et al., 2012; Norton et al., 2013). A different measure of depression and anxiety was used in Paper I, GADS, so this would not explain those findings. In that study, the participants were elderly men. Studies have found that elderly individuals are more likely to have mixed anxiety and depression (Byers et al., 2010; Flint, 1994). Despite this, only 6.9 percent of the sample from Paper I qualified for both anxiety and depression.

4.2 Depression and antidepressants

Depression is among the most common mental disorders in the world (Vos et al., 2020), causes a lot of suffering and damages in terms of economic costs. It is also associated with increased risk of CVD, which is among the most common cause of death and disability globally. Pharmacological treatment for depression involves antidepressant medication, and there is a need to demonstrate that this treatment is safe in terms of cardiovascular risk. The results from Paper III supports the notion that antidepressants do not increase risk of CVD. Of the studies that reported harmful effects of antidepressants, most attributed these effects to TCAs rather than SSRIs. Thus, the results support earlier studies that report reductions in CVD risk from SSRIs and antidepressants in general (Alqdwah-Fattouh et al., 2020; Kimmel et al., 2011), do not support other findings that antidepressants are unrelated to, or increase the risk of, CVD (cf. Hamer et al., 2011; Jang et al., 2020). In Paper III we analysed TCAs, SSRIs and other antidepressants separately and found that TCAs and SSRIs were related to a decreased risk of subsequent MI. An implication of this is that

both TCAs and SSRIs are cardioprotective. Nevertheless, due to the limitations of the study, like the lack of independence among the antidepressant groups, such a conclusion is probably premature. While the body of research on antidepressants and CVD has great heterogeneity in their results, SSRIs have more often been shown to be cardio-protective or at least not cardio-toxic. Thus, at least SSRIs are probably safe in terms of MI. There also does not seem to be a sex difference in terms of cardiovascular effect of SSRIs. Health care professionals should not be reluctant to prescribe antidepressant medication due to fear of increasing risk of MI.

Compared to anxiety, research has more unequivocally established depression as an independent risk marker of CVD (Gan et al., 2014; Harshfield et al., 2020; Rugulies, 2002). The results from Papers I and II support this finding. Paper IV suggests that personality may be part of the reason depression is linked to CVD. Personality has rarely been included in studies of depression on CVD.

4.3 Dispositions and personality

In Paper IV, extraversion was associated with increased risk of stroke for women, while neuroticism was associated with increased risk of MI for men. This partially replicated the results of a study by Jokela et al. (2014). They found that extraversion was related to increased risk of stroke mortality while neuroticism was related to increased risk of CHD mortality. Taken together, this indicates that neuroticism and extraversion are linked to different cardiovascular endpoints: CHD and CER respectively. Some studies have failed to find a relationship between personality and CVD: Nakaya et al. (2005) examined the links between the Eysenck personality traits and CHD and stroke in a large, prospective cohort design with extensive adjustment for confounding variables, and found no associations. They did not analyse men and women separately, however. A later study using the same sample found that psychoticism, but not neuroticism nor extraversion, was related to increased risk of CVD

(Narita et al., 2020).

Building on the previously reported findings that associated anxiety and depression with CVD, personality may be a relevant factor. Spectrum models of personality and psychopathology indicate that traits and disorders have a shared aetiology and that they exist on a spectrum (Klein et al., 2011; Widiger & Smith, 2008). This perspective could help explain why the addition of personality traits to the statistical models predicting CVD reduced the explanatory ability of anxiety and depression in Paper IV. In this view, the traits and the disorders are partially overlapping concepts, and the inclusion of both would lead them to "steal" explanatory ability from one another. The HADS has demonstrated high stability over several years, which could indicate that it reflects a more dispositional factor (Langvik & Hjemdal, 2015).

Aetiological models of personality and psychopathology may also explain this result. In these models, personality traits could affect CVD indirectly via their effect on depression and anxiety. To establish such an indirect effect, future studies using mediation analyses are needed. The tripartite model of Clark and Watson (1991) asserts that anxiety and depression share a common symptom cluster of negative affect. This negative affect has substantial theoretical overlap with neuroticism and extraversion. A central aspect of extraversion is positive emotions, while a central aspect of neuroticism is depressed mood. Following this, it is possible that the observed associations of anxiety and depression with CVD is actually an indication of personality's effect on CVD. Evidence for this is seen in Paper IV, as the inclusion of personality traits in the models render the previously observed associations of anxiety and depression attenuated. This is also in line with the results of Čukić and Bates (2015), that indicated that neuroticism was associated with CVD and could explain the association between depression and CVD.

4.4 Sex and gender differences

While we did not discern any sex-related differences in the relationship between antidepressant use and MI risk in Paper III, we observed unique personality differences among the sexes in Paper IV: specifically, extraversion was related to stroke risk for women, and neuroticism was related to MI risk for men.

Here, context has been shown to be important. Hagger-Johnson et al. (2012) found that high levels of neuroticism increased the risk of CVD mortality only for women that had low SES, while for high SES women it decreased the risk of CVD. SES was not assessed in any of the papers. Including it might have revealed similar patterns.

A recent cross-sectional study revealed elevated risks of MI for transgender women compared to cisgender women and for transgender women compared to cisgender women and cisgender men, even when controlling for traditional risk factors (Alzahrani et al., 2019). They are also at increased risk of depression (Witcomb et al., 2018). As such, even though this demographic represents a very small percentage of the global population, these individuals may have a unique risk profile that could warrant future studies.

Due to the many proposed mechanisms for sex differences in antidepressant effect (LeGates et al., 2019), we were surprised to not find any differences in Paper III. Female sex hormones are among the proposed reasons for why there could be sex differences. Thus, menopause would cause women and men to become more equal, as it decreases the production of sex hormones in women. In our paper we did not adjust for menopause specifically, and doing so could potentially have obscured differences that existed for younger participants.

There are sex-specific differences in the distribution of personality traits and in the prevalence of both anxiety and depression. Women are more likely to develop

depression (Seedat et al., 2009), and they tend to have higher scores on neuroticism and some facets of extraversion (Schmitt et al., 2017). Based on this, they are more at risk of CVD in the first place, as these psychological variables were shown to be related to increased risk of MI and stroke. Though extraversion's relation to stroke was only demonstrated for women. In Paper IV, men had a significantly higher risk of MI than women, but there was no sex difference in the risk of stroke (see Table 2 in Paper IV), which underscores the specificity of specificity in CVD outcomes.

4.5 Specificity

As the literature review of Paper II revealed, there is large heterogeneity in the methods and measurements involved in studies of psychological variables and CVD. This is undoubtedly a hindrance when comparing papers and study results. Despite this, it is unlikely to be an easy solution to this problem. There will always exists disagreement about which measurement tool is the best. Even what has been called the gold standard scales of depression measurement, the Hamilton Depression Rating Scale, has been criticised for methodological flaws and for no longer reflecting the content of the current definition of depression (Bagby et al., 2004). Another consideration is the trade-off between quality and ease of use. In a large study, researchers are incentivised to include many instruments and measurements to maximise the potential for research. As such, they are inclined to include shorter scales over longer ones. In this view it is more tempting to include the 14-item EPQ rather than a full 240-item instrument measuring FFM traits, for instance.

Related to that of the instrument being used, is the operationalisation of the variables in question. Depression and anxiety can be considered in terms of its related disorders, or as occurring on a continuum of levels ranging from normal to clinical (Thurston et al., 2013). While institutionalised diagnoses such as the DSM 5 diagnostic manual or ICD 11 medical classification system are beneficial when considering

them to be disorders, there are disadvantages when diagnostic contents differ with the state of the systems; as an example, the DSM-5 allows for two individuals with separate, non-overlapping symptoms to be diagnosed with the same disorder, major depressive disorder (American Psychiatric Association, 2013). To further illustrate this point, in a study of more than 3000 patients seeking treatment for major depressive disorders, Fried and Nesse (2015) found 1030 unique symptom profiles, and the most common profile applied only to 1.8 percent for the sample. Mirroring the categorisation of diagnoses, it is also common to use sum-scores to measure anxiety and depression. These sum-scores are then collapsed into discrete, binary categories. As it is likely that the mechanisms underlying anxiety or depression are similar for both subclinical and clinical levels of anxiety, this is not always a good strategy (Thurston et al., 2013). Nicholson et al. (2006) did not include continuous measures of depression in their meta-analysis and suggests that this might have led to both over- and underestimations of the effects of depression.

Related to this, most of the research on personality and CVD use types A and D as the measurement of personality. Two of the main criticisms of type D personality in particular is that it should be operationalised on a continuous level instead of a categorical one and that it overlaps with other facets of personality. Type D personality combines the social inhibition and negative affectivity facets of extraversion and neuroticism (De Fruyt & Denollet, 2002; Denollet & Brutsaert, 1998). These facets should be investigated separately, instead of as a composite measure which would obscure effects attributable to each facet.

It is also worth mentioning that the research in the field vary according to which cardiac outcome or endpoint they consider. At the most general, they consider CVD (cf. Hillebrand et al., 2013). Others focus on the sub-types of CVD, like CHD (Nicholson et al., 2006) or CER (Tully & Baune, 2014), or subtypes of those again, like MI (Gan et al., 2014). Some studies distinguish between mortality and morbidity associ-

ated with CVD, or study only one of them. Other consider cardiac risk scores, estimating CVD risks based on establish risk norms (D'Agostino et al., 2008). Findings from a study of CVD cannot automatically be applied to MI and vice versa. Despite this, there are shared components of these constructs, and knowledge of links between anxiety and MI can be informative when considering heart failure, even if it cannot be directly applied to it uncritically.

The perfect instrument to measure anxiety, depression or personality does not exist, and likely never will. There are also benefits of using various instruments to measure the same concept. For instance, the HADS is designed to not measure somatic symptoms of anxiety or depression. If anxiety and depression measured using the HADS do not show similar relations to CVD as expected from studies using different measures of anxiety and depression, this could indicate that the somatic components of anxiety and depression is essential for the cardiovascular effect.

4.6 The question of causality

As Herbert (2014) pointed out, some researchers avoid using words implying causation, preferring to refer to associations instead. The reason for this is that demonstrating causation is harder than demonstrating a simple association. Especially since causation traditionally has been demonstrated via experimental studies, and many authors thus feel that observational studies are unable to demonstrate causation. Since many epidemiological studies are observational in nature rather than experimental and randomised, this is a cause for reservation in terms of using the term cause. However, merely demonstrating a correlation between a variable and a health outcome is rarely of interest. The association is important only if there is a reason to believe that the variable affects or causes the outcome, to some extent. While establishing causation is difficult, it is regardless often "the ultimate objective" (Herbert, 2014, p.242).

It is a challenge to establish causality. Among the most well-known guidelines for doing so determining causation are the Bradford Hill criteria, also known as Hill's criteria for causation (Hill, 1965). Hill outlined nine aspects of an association to identify a causal relationship. He stressed that not all nine had to be present to determine causality, and that they should not be considered to be a checklist. These criteria are exhaustive and demonstrating all of them for a specific set of predictors and outcomes is more or less impossible; because causality must be documented in different samples at different times using different measures and methodologies, establishing causation is a task that falls to the greater researching community, rather than to a single study author. It is therefore understandable that the single study author would be reluctant to pronounce a link as being anything more directionally charged than "an association". Yet, as Herbert (2014) points out, researchers would not conduct studies if they did not suspect some sort of causal effect.

Even though Papers I–IV fall into the category of studies that cannot demonstrate anything beyond correlation, they are part of a larger body of research investigating the aetiology of psychological risk factors and CVD. The aim of the researchers in this field is to demonstrate whether depression or anxiety causes CVD, and while several studies initially indicated that anxiety is linked to increased CVD risk, the results of other studies suggest that this link is confounded by depression, because the effect of anxiety often disappears when depression is included in the model.

4.7 Limitations and strengths

In addition to the limitations of causality delineated above, there are additional limitations and strengths of this thesis.

Throughout Papers I and III–IV, a limitation of the study designs was that anxiety and depression were not assessed or diagnosed by a certified clinician. Instead, two sets of scales measuring anxiety and depression were used. In Paper I, the GADS

indicated those that had a fifty percent chance of having a clinically significant disturbance. In terms of generalising to individuals suffering from depression, it would have been preferable to confirm this diagnosis with a certified clinician conduct a diagnostic interview to ascertain a diagnosis. In Papers III–IV we instead considered anxiety and depression as an indication of the level of symptoms of each disorder. As both depression and anxiety are something that exists along a continuum and is present in various degrees among individuals, this can make the findings more generalisable. Instead of focusing mainly on those who have (likely) clinical levels of depression or anxiety, the results are more generally applicable.

Some studies have described the validity of the HADS and the GADS as good (Bjelland et al., 2002; Djukanovic et al., 2017; Kiely & Butterworth, 2015; Mackinnon et al., 1994), while others have described it as poor (Cosco et al., 2012; Koloski et al., 2008; Therrien & Hunsley, 2012). Both instruments have been suggested to measure a unified dimension of general distress instead of two separate distress constructs (Cosco et al., 2012; Koloski et al., 2008). If depression and anxiety as measured by the GADS and HADS in Papers I, III and IV is more appropriately utilised as a composite measure instead of separate measures, this could explain why anxiety was not shown to be associated with CVD as could be expected from meta-analyses like that of Batelaan et al. (2016).

Likewise, the EPQ that was used to measure neuroticism and extraversion in Paper IV is not the most commonly used personality inventory and is not based on the FFM, which is one of the major current personality taxonomies (Costa & McCrae, 1992). The EPQ does not capture all the five traits in the FFM, so any links between conscientiousness, agreeableness and openness to experience with CVD remains to be explored. Conscientiousness in particular is of interest, as the trait has been linked to various health-promoting behaviour like medicine adherence and exercise (Hoyt et al., 2009; Molloy et al., 2014), and has been found to be cardio-protective (Jokela

et al., 2014).

Considering one of the goals of the thesis was to assess sex-specific risks, the fact that the sample in Paper I only included men is a limitation. This facilitated an examination of the effects of anxiety on CVD risk in an international sample, however, and complemented the studies on Norwegian samples in presented in Papers III and IV. Bearing in mind the limitations of the GADS and HADS described above, another strength was the use of two different instruments to measure anxiety and depression. This allowed for the comparison of different measures in different samples. Effects that are seen across more samples and operationalisations are inherently more valid.

The size of the samples included in Papers I, III and IV is among the strengths of the thesis. Small samples do not allow for statistical analyses with enough statistical power to detect significant effects (Ioannidis, 2005). When dealing with outcomes that are relatively infrequent, a large sample is also necessary to detect enough instances for analyses. For example, while CVD is among the most common diseases, we would still expect less than one percent of the sample to develop CVD during the study period.

Another strength was the ability to link data from the HUNT Study to national health registry data. This allowed for the use of time series data (time to death from MI or stroke) in Paper IV, as well as analysing recorded prescriptions of antidepressants in Paper III. The late genesis of the NorPD that recorded medication prescriptions limited the follow-up time for Paper III, however.

4.8 Future research

Neither Papers I, III nor IV found a relationship between anxiety and CVD when adjusting for depression. On their own, they imply that there is no effect of anxiety on CVD that cannot be explained by depression instead. However, the only way to find out is to replicate the findings under similar and different conditions. Single studies

will be beneficial when enough has been published that researchers can meta-analyse and systematically review them. This will help determine whether the findings of the single studies were more likely true in general, true for only a specific population, or the result of a statistical type I or II error. Of the recent meta-analyses on anxiety and CVD, only two adjusted for depression and both found that the association between anxiety and CVD remained significant (Batelaan et al., 2016; Tully et al., 2015). It still remains to be determined which of the sub-types of anxiety are related to CVD (Tully, 2017), and future studies should examine these sub-types. More single studies of better quality (e.g., medical records for CVD instead of self-report) also lays the foundation for new meta-analyses of better quality.

Related to this and on a more general note, this thesis notes the importance of specificity in terms of CVD outcomes. Depression and anxiety seem to be more related to MI than stroke, for instance. Analysing cardiac outcomes at the broad level of CVD might obscure effects visible at the lower diagnostic levels. As such, future research should focus on specific CVD sub-types.

There is a dearth of research on the role of personality in the genesis of CVD and a significant portion of the extant research uses type D terminology which seems to be outdated with diminishing support for its validity. Future research should focus on the more supported personality traits. Extraversion and neuroticism may have cardiovascular effects and should be focused on. Finally, a benefit of using the FFM framework is that it allows sub-facets of the traits, such as positive emotions from extraversion and tendencies towards anxiety and depression from neuroticism, to be studied.

4.9 Conclusion

Anxiety was not found to be a risk marker for CVD independent of depression. This relationship was assessed with CHD, CER, MI and stroke in samples from both Nor-

way and the United States. In general, depression demonstrated stronger associations with CVD than anxiety did. Antidepressant was related to a decreased risk of MI, and this decrease seemed to be caused by SSRIs and TCAs, but not other antidepressants. No sex differences were found in the reduction of MI risk and as such, antidepressants seem safe to use for both men and women in terms of cardiovascular risk. Extraversion and neuroticism were found to be partially related to CVD. Extraversion was associated with an increased risk of stroke for women, while neuroticism was associated with increased risk of MI for men. Including extraversion and neuroticism attenuated the previously observed effects of anxiety and depression. This may indicate that anxiety and depression represent some dispositional component that overlaps with personality or that personality affects both anxiety and depression and CVD. Even though the different associations of extraversion and neuroticism with stroke and MI were the only sex differences we found, sex remains an important focus for future studies, because men and women have different cardiovascular risk profiles.

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Paper I

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Anxiety as a risk factor for cardiovascular disease independent of depression: a prospective examination of community-dwelling men (the MrOS study)

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ABSTRACT

Objective: Anxiety and depression have been linked to increased risk of cardiovascular disease (CVD). Whether anxiety is a risk factor independent from depression, and if associations are limited to specific CVD outcomes remains unclear. **Design**: Participants ($N = 3135$) of the prospective Osteoporotic Fracturs in Men Sleep ancillary study were community-dwelling men (age $\geq$ 65) living in the US. **Main outcome measures**: The Goldberg Anxiety and Depression Scales, coronary heart disease (CHD) and cerebrovascular disease (CER). We used Cox proportional hazards models to calculate adjusted hazard ratios and 95% confidence intervals. **Results**: During 12 years of follow-up, we accrued 612 cases of CHD and 291 cases of CER (incident or repeat-event). Overall, we observed no association between anxiety or depression and CER. Anxiety was significantly associated with CHD, but this effect was attenuated after controlling for depression and covariates. Depression was significantly associated with CHD after similar adjustments. For men without prior history of CVD, neither anxiety nor depression were associated with incident CHD. **Conclusions**: Anxiety was not a significant independent predictor of CHD or CER, suggesting that previous findings of anxiety as a risk factor of CVD might be attributed to failure to control for the effect of depression.

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Introduction

Cardiovascular disease (CVD), including coronary heart disease (CHD) and cerebrovascular disease (CER), is the world's leading cause of death (Piepoli et al., 2016). With some of the most established risk factors for CVD (e.g. smoking, high cholesterol levels, hypertension) on the decline (Piepoli et al., 2016), others, like obesity, are rising (Blüher, 2019), and researchers also acknowledge the importance of psychosocial risk markers including anxiety and depression (Albus, 2010; Cohen et al., 2015; Piepoli et al., 2016). Current CVD prevention guidelines suggest screening for both anxiety and depression to identify those at greatest risk (Piepoli et al., 2016), even though the status of anxiety as a risk factor of CVD is not as well established as it is for depression (Albus, 2010; Cohen et al., 2015). To close this gap, during the last decade, there has been an increased focus on studying the connection between anxiety and the development of CVD (Batelaan et al., 2016; Roest et al., 2010; Stewart et al., 2016; Tully et al., 2013). However, evidence remains mixed. Although meta-analyses (Emdin et al., 2016; Roest et al., 2010) have presented evidence of anxiety associated with an increased risk of CVD, the studies have been criticised for failing to take into account the effects of depression (Cohen et al., 2015; Tully et al., 2016). Anxiety and depression, both in terms of symptom reporting and diagnosis, are often comorbid, starting from childhood onwards, with a stronger tendency for anxiety being a precursor of depression than the other way around (Bruce et al., 2016; Cummings et al., 2014). Some researchers have suggested that depression is the main driver of the perceived relationship between anxiety and CVD risk due to the high comorbidity (Miloyan et al., 2016). Others have even suggested that anxiety has a protective effect on CVD risk (Hagger-Johnson et al., 2012; Langvik & Nordahl, 2014; Meyer et al., 2015; Parker et al., 2011; Pérez-Piñar et al., 2017). While anxiety and depression share a distinct neuroanatomical profile, specific regional brain volumes are differently associated with anxiety and depression (van Tol et al., 2010). Further, while depression is associated with determinantal health behaviors, anxiety is on the other hand positively associated with health protective behaviors in cardiac patients (Benyamini et al., 2013). Depression is linked to CVD both through behavioral factors and physiological mechanisms such as inflammatory response, platelet reactivity (Bucciarelli et al., 2020) and autonomic nervous system dysregulation (Tolentino & Schmidt, 2019). Research on pathophysiological mechanisms linking anxiety and CVD has been limited (Alvarenga & Byrne, 2016) and mixed (Ransing et al., 2017). Depression, but not anxiety is associated with cardiac risk factors like plasma triglycerides, glucose, and insulin resistance (Holt et al., 2013). For both platelet activation and inflammation, there is stronger evidence for the link to depression compared to anxiety (Huffman et al., 2010), further supporting an investigation of the role of anxiety as a risk marker independent of depression.

In one of the most comprehensive studies to date, a recent meta-analysis (Batelaan et al., 2016) that adjusted for depression found anxiety to be associated with an increased risk of CVD. While some have shown that anxiety is an independent risk factor of CVD events, when controlling for depression and conventional risk factors (Stewart et al., 2016), there is at present inconclusive evidence of an independent association of anxiety with incident CVD (Tully, 2017). Thus, there is a need for more

studies examining the independent effect of anxiety on the risk of incident CVD, accounting for levels of depression.

Inconclusive or conflicting findings may also be attributed to different CVD outcomes combined as the main outcome variable, heterogeneous operationalisation of anxiety (i.e. different sub-types of anxiety having specific CVD-outcome relations), or the failure to differentiate between anxiety and depression as an etiological or prognostic marker (Tully et al., 2013). Research suggests that phobic anxiety has a stronger linkage to CVD than other sub-types, and that anxiety is unrelated to MI, but may be more important for other CVD outcomes (Alvarenga & Byrne, 2016). Further, gender differences are relevant not only for risk estimates, but also for the association between anxiety, depression and cardiovascular risk factors (Holt et al., 2013; Langvik & Nordahl, 2014). Sex differences in physiopathology and gender-differences in biological responses to mental stress (Bucciarelli et al., 2020) warrant the study of psychological risk-markers of CVD separately for men and women.

In the present study, we investigated whether anxiety is independently associated with CVD in an elderly, male population. In line with the reviewed literature, we hypothesised that depression increases risk of incident and repeat event CHD and CER, and that any association between anxiety and these outcomes will be attenuated when including depression in the model. In our models, we adjusted for common risk factors of CVD: age, BMI, cholesterol, blood pressure, physical activity, alcohol consumption, smoking status and diabetes (Piepoli et al., 2016; Reid & Owen, 2016). Other adjustments were included because their association with CVD risk: sleep quality (Cappuccio et al., 2011), education (Piepoli et al., 2020) and ethnicity (Kurian & Cardarelli, 2007). We included antidepressant use as a covariate, as it has been implicated in CVD risk (Glassman & Bigger, 2010; Nezafati et al., 2015).

Materials and methods

Sample and procedure

Participants ($N = 5994$) were recruited over a 25-month period from 2000 through 2002 as part of the Osteoporotic Fractures in Men Study (MrOS; http://mrosdata.sfcc-cpmc.net). The current study sample is based on the MrOS Sleep Study, an ancillary study that performed initial assessments from December 2003 to March 2005 among 3135 of the 5994 participants enrolled at MrOS baseline. Forty of these participants were excluded because they had missing values on central variables. The MrOS Sleep Study had a target recruitment number of 3000 participants (Mehra et al., 2007). See Figure 1 for a flow diagram of participants in the study. The study design, baseline characteristics and recruitment process have been previously described (Blank et al., 2005; Orwoll et al., 2005). In brief, the participants were community-dwelling men of 67 years or older at the time of the sleep study. As osteoporosis was the main focus in the MrOS study, participants had to be able to walk without assistance of another person and must not have had a bi-lateral hip replacement to be eligible. Participants were recruited from populations near six clinical sites across the US (Birmingham, AL; Minneapolis, MN; Palo Alto, CA; Pittsburgh, PA; Portland, OR, and San Diego, CA). Information about participants was gathered through self-administered questionnaires,

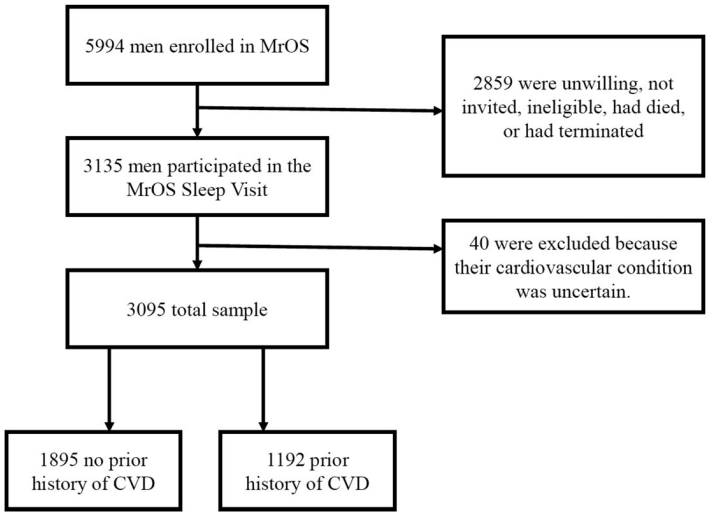

Figure 1. Flow diagram of participant recruitment.

interviewer-administered questionnaires and clinical examinations. The Sleep Study participants underwent comprehensive objective and subjective sleep assessments, and completed self-administered questionnaires related to anxiety and depression. This subset of the total sample formed the basis of the analyses in this article. All participants completed informed consent, and the study protocols were approved by Institutional Review Boards at each of the participating clinic sites.

Instruments

Anxiety and depression

The Goldberg Anxiety and Depression Scales (GADS) were used to measure anxiety and depression (Goldberg et al., 1988). Anxiety and depression were measured respectively using 9-item scales, where for each item participants indicated either the presence or the lack of symptoms. Examples of items were: "Have you felt keyed up, on edge?" (Anxiety) and "Have you had low energy?" (Depression). For each 9-item scale a summary score was generated by adding the number of items in which a presence of symptoms was indicated. A depression score of two or more or an anxiety score of five or more was used to indicate that the participant had a 50% chance of having a clinically important disturbance (Goldberg et al., 1988). The instrument has been recommended for use in epidemiological investigations as a short, valid and acceptable method of detecting heightened levels of anxiety and depression in elderly people (Koloski et al., 2008; Mackinnon et al., 1994).

Cardiovascular outcomes

Participants were followed for potential incident cardiovascular events by tri-annual questionnaire and/or phone. They were contacted every four months and had an overall response rate of more than 99%. Participants were asked about hospitalization or

treatment for any CVD-related condition during the preceding 4-month interval. Medical records were obtained for all potential cases, and each case was centrally adjudicated by the MrOS Coordinating Center at the University of California, San Francisco and California Pacific Medical Center. Fatal events were further adjudicated by obtaining the death certificate or hospital records at the time of death, or by interview with the next of kin if the event did not result in hospitalization. The adjudicators were certified cardiologists using protocols that had successfully been employed at previous trials and studies of CVD (Grady et al., 1998). Follow-up time was through February 28th, 2015. The average time to a CHD event was 8.0 ($SD = 3.4$) years, 8.5 ($SD = 3.0$) years to a CER event. Coronary heart disease (CHD) includes any events in the following categories: acute myocardial infarction, coronary artery bypass surgery, ischemic congestive heart failure, mechanical coronary revascularization, ST and non-ST elevation MI, hospitalisation for unstable angina, sudden CHD death or other CHD event. Cerebrovascular (CER) events included stroke (residual after 24 hours) or transient ischemic attacks (TIA, no residual after 24 hours).

Model adjustment

Physical activity was measured using the Physical Activity Scale for the Elderly (PASE; Washburn et al., 1993). It was specifically designed to measure physical activity in the elderly, therefore including fewer items asking about sports and recreational activities, and more items about everyday activities. Participants were asked whether or to what degree they were involved in 12 types of activities during the last seven days, and weights were applied, reflecting the strenuousness of the activity. In the current sample, the scores on PASE ranged from 0 to 592. Sleep quality was measured using the Pittsburgh Sleep Quality Index (Buysse et al., 1989). Nineteen questions measured sleep quality, yielding a continuous scale from 0 to 21. Body mass index (BMI) was calculated based on measured height and weight taken of the participants at the sleep visit (kg/meters^2). Serum samples were taken from the participants to measure oxidised LDL (cholesterol), measured in "milli units per litre" (Harrison, 2014). Resting blood pressure was measured using mercury sphygmomanometer. Self-reports were used to ascertain the number of alcoholic beverages a participant consumed a week (0-2, 3-13, more than 13), whether they had ever had diabetes or used antidepressants and their current cigarette smoking status (yes, no, or former).

Analysis

We used Stata/MP v. 15 for Windows to calculate Cox proportional hazards models. The dependent variable was time from clinic visit to fatal or nonfatal CVD endpoints. Separate models were run for CHD and CER outcomes. We performed three sets of analyses. In the first set we analysed the whole sample and added prior history of CVD as a covariate. In the second set, we analysed the subset of the sample that had no prior history of CVD (incident CHD and CER). In the third set, we analysed the subset of the sample that had experienced a previous CVD event (repeat event CHD and CER). As CHD and CER share many of the same risk factors, CVD was used as a general stratum instead of history of CHD or CER.

In Model 1, anxiety and depression were entered separately into the model to examine their individual effects. In Model 2 they were entered together to determine their independent effects in the presence of the other condition, while in Model 3 they were entered together in addition to all covariates. The covariates included an a-priori set of established risk markers of CVD according to current guidelines (Piepoli et al., 2016). Education, ethnicity, diabetes, use of antidepressants, smoking status and alcohol use were entered into the model as categorical variables, while age, blood pressure, cholesterol levels, BMI, sleep quality and activity were entered as continuous variables. Kaplan-Meier curves were produced to show the unadjusted probability of a CHD/CER event as a function of anxiety.

Results

The baseline characteristics of the sample are presented in Table 1, for the overall cohort, as well as stratified by outcome category (no CVD event, CHD event and CER event). The mean body mass index was 27.17 ($SD = 3.83$). At baseline (sleep visit 1), 3095 participated, and the mean age was 76.38 ($SD = 5.54$). Of those, 2078 participants did not experience any CVD events by the end of the follow-up period, while 612 experienced one or more CHD events and 291 experienced one or more CER events. Of the total sample, 277 (8.75%) had an anxiety score above 5, corresponding to a 50% chance of having a clinically significant disturbance. Among the no CVD event group, the proportion of participants with GADS-A ≥ 5 was 8.12%, compared to 11.11% and 8.65% in the groups with CHD events and CER events, respectively. Of the total sample, 1042 (33.81%) had GADS-D ≥ 2. The proportion having GADS-D ≥ 2 in the no CVD event group was 31.30%, while it was 43.42% in the CHD event group and 32.07% in the CER event group. A total of 215 (6.9%) men had both elevated anxiety and depression scores, and the association between anxiety and depression was significant, but moderate, $\chi^2 = 282.59$, $V = .30$, $p < .001$.

Of the total sample, 38.61% had a previous diagnosis of CVD before the start of the study. Prevalence of prior diagnosis of CVD was 31.98% for the no CVD event group, 58.10% for the CHD event group and 47.93% for the CER event group.

Anxiety and risk of CHD

The results from the survival analyses can be seen in Tables 2–4. Figures 2–4 feature the Kaplan-Meier survival curves showing the time to CHD event in Model 1 for those with and without anxiety, in the total sample and the two sub-sets.

In the unadjusted model (Model 1) for the total sample, anxiety was statistically significantly associated with the risk of having a CHD event, with a hazard ratio of 1.41, 95% CI [1.10, 1.83], $p = .008$. After controlling for depression (Model 2), the hazard ratio of anxiety decreased to 1.06, 95% CI [0.80, 1.39], $p = .693$. In this model, depression had a significant hazard ratio of 1.68, 95% CI [1.41, 1.99], $p < .001$. Results were similar in Model 3 after controlling for all covariates (age, education, race/ethnicity, diabetes, antidepressant use, BMI, cholesterol/oxidised low-density lipoprotein, smoking status, drinking habit, physical activity and sleep quality), in which no association

Table 1. Baseline characteristics of the sample.

Variables	Total sample (N = 3095)		No CVD event (N = 2078)		CHD event (N = 612)		CER event (N = 291)	
	M / n	*(SD) / (%)*	*M / n*	*(SD) / (%)*	*M / n*	*(SD) / (%)*	*M / n*	*(SD) / (%)*
Age	76.38	(5.54)	76.01	(5.51)	77.12	(5.44)	77.55	(5.65)
BMI	27.17	(3.83)	27.01	(3.73)	27.60	(4.06)	27.04	(3.57)
Cholesterol (OLDL mU/L)	44071.11	(12276.14)	44056.05	(12284.32)	43958.50	(12124.63)	43875.78	(11833.54)
Blood pressure	126.94	(16.32)	125.91	(15.68)	129.56	(17.85)	129.95	(17.65)
Sleep quality	5.61	(3.26)	5.51	(3.20)	6.08	(3.59)	5.35	(3.05)
Physical activity	145.76	(72.08)	147.58	(72.20)	141.72	(72.81)	144.68	(71.57)
Anxiety	270	(8.75%)	168	(8.12%)	68	(11.11%)	25	(8.65%)
Depression	1042	(33.81%)	648	(31.30%)	264	(43.42%)	93	(32.07%)
Previous CVD	1192	(38.61%)	663	(31.98%)	355	(58.10%)	139	(47.93%)
Education								
HS	652	(21.07%)	407	(19.59%)	162	(26.47%)	54	(18.56%)
C	1267	(40.94%)	833	(40.09%)	256	(41.83%)	126	(43.30%)
GS	1176	(38.00%)	838	(40.33%)	194	(31.70%)	111	(38.14%)
Race/ethnic category								
White	2 780	(89.82%)	1 852	(89.12%)	566	(92.48%)	262	(90.03%)
African American	118	(3.81%)	85	(4.09%)	14	(2.29%)	10	(3.44%)
Asian	100	(3.23%)	77	(3.71%)	10	(1.63%)	10	(3.44%)
Hispanic	59	(1.91%)	38	(1.83%)	13	(2.12%)	7	(2.41%)
Other	38	(1.23%)	26	(1.25%)	9	(1.47%)	2	(0.69%)
Diabetes	409	(13.22%)	238	(11.46%)	111	(18.14%)	43	(14.83%)
Antidepressant use	246	(7.95%)	151	(7.27%)	62	(10.13%)	22	(7.56%)
Smoking status								
no	1 223	(39.54%)	838	(40.35%)	228	(37.25%)	104	(35.86%)
past	1 806	(58.39%)	1 198	(57.68%)	376	(61.44%)	176	(60.69%)
current	64	(2.07%)	41	(1.97%)	8	(1.31%)	10	(3.45%)
Alcohol intake, drinks/week								
0-2	1 826	(59.32%)	1200	(58.03%)	388	(63.92%)	168	(57.93%)
3-13	1 079	(35.06%)	745	(36.03%)	199	(32.78%)	105	(36.21%)
≥14	173	(5.62%)	123	(5.95%)	20	(3.29%)	17	(5.86%)

Note. HS = high school or less, C = Some college or less, GS = Some graduate school or graduate school. CVD = cardiovascular disease. CHD = coronary heart disease. CER = cerebrovascular disease. BMI = body mass index. OLDL = oxidised low-density lipoprotein.

Table 2. Hazard ratios for cardiovascular diseases in the total sample.

	Model 1 ($N = 3049$)		Model 2 ($N = 3043$)		Model 3 ($N = 2920$)	
Predictors	HR	95% CI	HR	95% CI	HR	95% CI
	Coronary heart disease					
Anxiety	1.41**	[1.10, 1.83]	1.06	[0.80, 1.39]	0.95	[0.71, 1.27]
Depression			1.68***	[1.41, 1.99]	1.33**	[1.10, 1.60]
Previous CVD					2.36***	[1.98, 2.82]
	Cerebrovascular disease					
Anxiety	1.07	[0.71, 1.62]	1.05	[0.68, 1.63]	1.11	[0.69, 1.77]
Depression			1.05	[0.80, 1.36]	0.94	[0.71, 1.26]
Previous CVD					1.52**	[1.18, 1.96]

Note. HR: hazard ratio. Model 1: Unadjusted. Model 2: Adjusted for depression. Model 3: Adjusted for all covariates. $^{**}p < .01$, $^{***}p < .001$.

Table 3. Hazard ratios in participants with no previous diagnosis of CVD.

	Model 1 ($N = 1875$)		Model 2 ($N = 1870$)		Model 3 ($N = 1798$)	
Predictors	HR	95% CI	HR	95% CI	HR	95% CI
	Coronary heart disease					
Anxiety	1.20	[0.75, 1.91]	0.97	[0.58, 1.61]	1.10	[0.63, 1.84]
Depression			1.33*	[1.003, 1.773]	1.10	[0.80, 1.50]
	Cerebrovascular disease					
Anxiety	0.69	[0.32, 1.48]	0.67	[0.31, 1.49]	0.71	[0.31, 1.61]
Depression			1.06	[0.72, 1.56]	0.95	[0.63, 1.43]

Note. HR: hazard ratio. Model 1: Unadjusted. Model 2: Adjusted for depression. Model 3: Adjusted for all covariates. $^{*}p < .05$.

Table 4. Hazard ratios in participants with history of CVD.

	Model 1 ($N = 1168$)		Model 2 ($N = 1167$)		Model 3 ($N = 1122$)	
Predictors	HR	95% CI	HR	95% CI	HR	95% CI
	Coronary heart disease					
Anxiety	1.24	[0.91, 1.69]	1.01	[0.73, 1.40]	0.87	[0.61, 1.25]
Depression			1.56***	[1.25, 1.94]	1.51**	[1.19, 1.93]
	Cerebrovascular disease					
Anxiety	1.23	[0.75, 2.02]	1.29	[0.76, 2.17]	1.67	[0.92, 3.02]
Depression			0.90	[0.62, 1.30]	0.97	[0.65, 1.46]

Note. HR: hazard ratio. Model 1: Unadjusted. Model 2: Adjusted for depression. Model 3: Adjusted for all covariates. $^{**}p < .01$, $^{***}p < .001$.

was observed between anxiety and CHD (HR = 0.95, [0.71, 1.27], $p = .730$), and the association between depression and CHD remained significant but somewhat attenuated with a hazard ratio of 1.33, 95% CI [1.10, 1.60], $p = .003$. When restricting the analyses to men with a prior history of CVD at baseline, depression was associated with an increased risk of repeat event CHD when adjusting for all covariates, HR = 1.51, 95% CI [1.19, 1.93], $p = .001$. Depression was significantly associated with incident CHD among those with no history of CVD (HR = 1.33 [1.003, 1.773], $p = .048$), however, this effect was attenuated when controlling for other covariates. Anxiety was not significantly associated with either incident or repeat event CHD.

The inclusion of anxiety (Model 2) only marginally altered the HR of depression on CHD in the group with no history of CVD, from 1.32 to 1.33. There was no change in the HR of depression on CHD in the total sample nor in the group with a prior history of CVD.

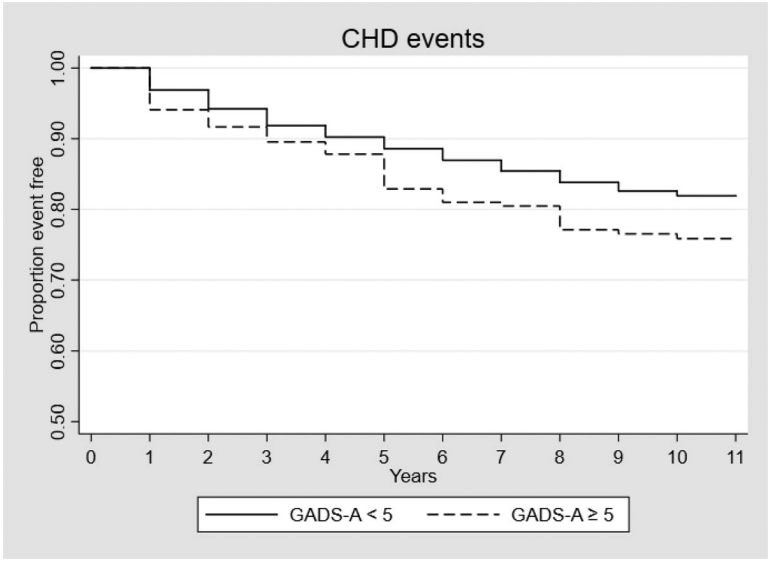

Figure 2. Anxiety and risk of CHD in total sample.

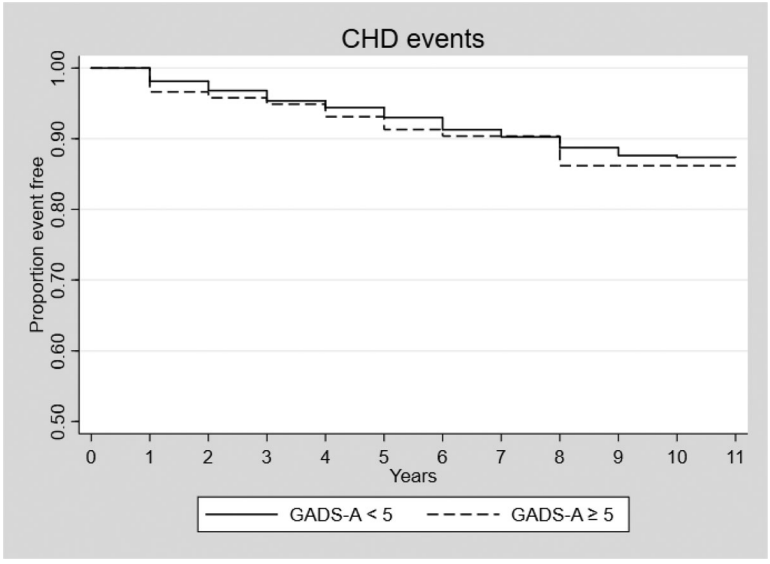

Figure 3. Anxiety and risk of CHD in sample with no previous diagnosis of CVD.

Anxiety and risk of CER

Neither anxiety nor depression had a significant effect on CER in any of the three sets of analyses (Tables 2–4).

Discussion

In the present study we found that anxiety increased the risk of CHD events among community dwelling older men. However, this effect was no longer significant when

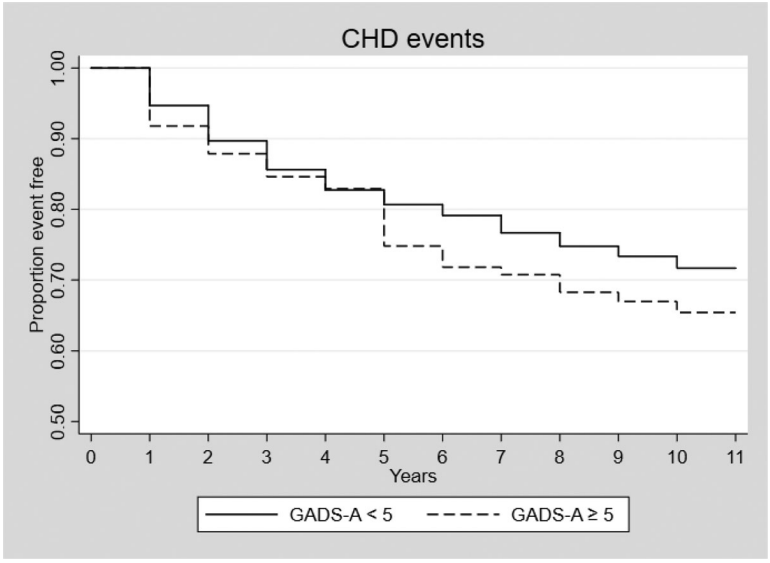

Figure 4. Anxiety and risk of CHD in sample with prior history of CVD.

controlling for depression, as hypothesized. Depression significantly increased the risk of incident and repeat event CHD even when controlling for anxiety and prior history of CVD, and other relevant control variables. Among those with no prior history of CVD, neither depression nor anxiety was a significant predictor after controlling for other variables. In contrast, among those participants with prior history of CVD, depression, but not anxiety, was associated with risk of CHD. Neither depression nor anxiety had a significant effect on the likelihood of experiencing a CER event in any of the analyses.

These results differ from the conclusions by recent meta-analyses that show an effect of anxiety on CVD, when controlling for the effect of depression (Batelaan et al., 2016; Tully et al., 2013). Anxiety and depression can be difficult to properly differentiate due to their shared components (Clark & Watson, 1991) and comorbidity (Jacobson & Newman, 2017). Characteristics of the current sample and instruments might explain why we observed different results compared to recent meta-analyses. Anxiety and depression were measured using the Goldberg Anxiety and Depression Scale (GADS), an instrument not used by any of the studies included in Batelaan et al. (2016), Emdin et al. (2016), Pérez-Piñar et al., (2017) or Roest et al. (2010). Compared to other measures (e.g. the Hospital Anxiety and Depression scale; Zigmond & Snaith, 1983), GADS has a stronger focus on somatic symptoms, and has less strict cut-off values. Our sample had a mean age of 76 years. Comparatively, only 7 of the 32 studies included in Batelaan et al. (2016) researched samples aged 65 years or older. Additionally, only men were included in the current study. When making comparisons to the meta-analyses, it should be mentioned that they all, with the exception of Emdin et al. (2016), present substantial heterogeneity, implicating that divergent results between our study and the meta-analyses could be expected.

Depression was associated with an increased risk of CHD, and this effect persisted when looking only at participants with prior history of CVD, though it was not

significant in the subset with no prior history of CVD when controlling for other variables. This is contrary to other studies showing depression to be an independent risk marker for incident CHD (Gan et al., 2014; Nicholson et al., 2006; Rugulies, 2002; Wu & Kling, 2016). Hence it is premature to conclude that depression is not an important risk factor for incident CHD. It might however suggest that the risk differs across populations. For instance, prior studies have found that depression was a stronger risk factor for women compared to men (Langvik & Nordahl, 2014). The current study indicates that risk factors of CVD may also differ across age groups, and that anxiety is less important compared to other risk markers among older men. The proportion of people who survive a CVD event is growing, though, which also makes knowledge about risk factors for a subsequent CVD event important.

The results underline the importance of specificity in research on the link between affective disorders and CVD, both in terms of the population of interest (prognostic vs. etiologic approach) and outcome. Depression was not associated with incident CHD in the group free of CVD at baseline, only with repeat event CHD. Further, the results varied across outcomes: While anxiety and depression variously showed some relation to CHD, an effect on CER was not observed. Studies variously use CVD or CHD as outcome, but the inclusion of CER events in a composite CVD outcome might obscure the results. The etiologies of CER and CHD are different (Widimský et al., 2013), hence affective disorders may affect them differently. For instance, 90% of MI patients share the underlying cause of their CHD (i.e. atherosclerotic plaque rupture with arterial thrombosis), while the causes of CER are more heterogenous (Widimský et al., 2013)

The majority of the previous studies on anxiety or depression have failed to control for the effect of the comorbid counterpart (Batelaan et al., 2016), making it difficult to draw conclusions about whether the effect is actually caused by the shared variance, or the other affective disorder. The study also supports increased specificity in choice of outcomes: While anxiety and depression variously showed some relation to CHD, an effect on CER was not observed.

One of the strengths of the study is the large sample used, another is that we controlled for all relevant confounders, both well-known ones such as age, smoking, cholesterol, blood pressure diabetes, BMI and physical activity (Piepoli et al., 2016) and more ambiguous ones such as antidepressant-use (Glassman & Bigger, 2010). Additionally, we controlled for the effect of the depression in analysing anxiety and performed separate analyses on participants with and without prior history of CVD. A limitation of this study is that it samples a rather homogenous population, namely older, primarily Caucasian men in the US, and the results therefore cannot be generalised to younger adults or women. The role of anxiety as an etiological and prognostic factor for women and in other age-groups warrants further investigation. Older men are more prone to CVD, which might bias the results compared to a more diverse sample. At the same time, the elderly are most likely to develop CVD, and thus, a particularly interesting group to study in the interest of reducing the general disease burden. Further, as psychological markers differ both in prevalence and CVD risk estimate among men and women, separate analysis for men and women are warranted (Langvik & Nordahl, 2014). Despite evidence of GADS having good psychometric qualities (Mackinnon et al., 1994), there are some limitations with the use of GADS. The

discriminant validity has been questioned due to high correlations between the two subscales of GADS (Therrien & Hunsley, 2012). Further, it has been suggested that the cut-off scores are too low, especially for depression (Koloski et al., 2008). In our sample, the prevalence and ratio of depression to anxiety cases was higher than expected based on the general prevalence in most populations (Bandelow & Michaelis, 2015; Hasin et al., 2018), but our result are similar to other studies using GADS in older samples (Koloski et al., 2008).

Conclusion

In the current study, elevated symptoms of anxiety were not a significant independent risk factor for CHD or CER, regardless of prior history of CVD status among elderly men. This supports the notion that relationship between anxiety and CVD observed previously might be explained by comorbid depression, particularly among older men. Though further research is needed to confirm these findings, results suggest it may be prudent to focus on treatment of depression to reduce risk of CHD among older men. Treatment of anxiety symptoms may have little effect on risk of CVD outcomes.

Disclosure statement

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Data findings

The data that support the findings of this study are openly available at MrOS Online: https://mrosdata.sfcc-cpmc.net.

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Anxiety as a risk factor for cardiovascular disease independent of depression: A narrative review of current status and conflicting findings

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Abstract

The aim of this paper is to summarise and evaluate the empirical support for the association between anxiety and cardiovascular disease (CVD) and to address challenges related to method and study design. We review results from meta-analyses and more recent findings on the association of anxiety and the risk of CVD. Depression and anxiety are often listed as psychosocial risk markers of CVD, but the role of anxiety as a risk factor for CVD has not received the same evidential support as the effects of depression. Through a narrative review we identified six meta-analyses as well as 15 recent large studies of anxiety and CVD that we summarise. Some of the conflicting findings may be artefacts of study design or population the sample is drawn from. Researchers should take care to be population specific, measurement specific and outcome specific, and to control for comorbid depression.

Keywords

anxiety, cardiovascular disease, coronary disease, review, stroke

Introduction

Anxiety disorders are the most prevalent group of psychiatric disorders worldwide (Pérez-Piñar et al., 2016) with a reported lifetime prevalence as high as almost 29% (Kessler et al., 2005). Cardiovascular diseases (CVD), especially Coronary Heart Disease (CHD), are the leading cause of death in Europe (Townsend et al., 2015), as well as in China (Zhou et al., 2016). Considering the massive impact of both anxiety disorders and CVD in terms of mortality and quality of life, further enquiry into a possible association between them appears both relevant and necessary. While research has mainly focused on depression, which is an obvious major psychiatric ailment, and has identified it as an independent risk factor for the development of CVD (Lichtman et al., 2014; Pan et al., 2011), the research on anxiety's association with CVD has not yielded the same conclusive results so far. The aim of this narrative review article is to summarise recent findings and challenges in the research field.

Methodology

We searched online for papers that examined the relationship between anxiety and CVD while controlling for the potential confounding effects of depression. Databases we searched were MEDLINE, Psychinfo, Global Health and Google Scholar, using these keywords: 'anxiety or anxiety disorder or generalised anxiety disorder or panic or panic disorder and cardiovascular disease or heart disease or heart attack or myocardial infarction or stroke'. We excluded papers that did not control for depression.

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Table 1. Key characteristics of discussed meta-analyses.

Study	Number of included studies	*N*	Results (95% CI)
Batelaan et al. (2016)	37	1,565,699	CVD: HR = 1.52 [1.36, 1.71]; Only studies adjusting for depression: HR = 1.57 [1.29, 1.90]
Celano et al. (2015)	44	30,527	Dic. Anxiety measure: Mortality: OR = 1.30 [0.98, 1.73]; Composite outcome: OR = 1.20 [0.91, 1.58]; Cont. Anxiety measure: Mortality: OR = 1.08 [0.90, 1.30]; Composite outcome: 1.21 [1.05, 1.39]
Emdin et al. (2016)	46	2,017,126	CV mortality: RR = 1.41 [1.13, 1.76]; CHD: RR = 1.41 [1.23, 1.61]; stroke: RR = 1.71 [1.18, 2.50]; HF: RR = 1.35 [1.11, 1.64]
Pérez-Piñar et al. (2017)	8	950,759	Stroke: HR = 1.24 [1.09, 1.41]
Roest et al. (2010)	20	249,846	CHD: HR = 1.26 [1.15, 1.38]; Cardiac mortality: HR = 1.48 [1.14, 1.92]
Tully et al. (2015)	12	1,131,612	CHD, panic disorder: adjusted HR = 1.47 [1.24, 1.74]. Excluding depression cases: adjusted HR = 1.64 [1.45, 1.85]

CVD: Cardiovascular disease; HR: Hazard ratio; Dic.: dichotomous; OR: Odds ratio; Cont.: continuous; CV: Cardiovascular; CHD: Coronary Heart disease; RR: Relative Risk; HF: Heart Failure.

While we mainly focus on general anxiety disorder and anxiety in general, we also discuss panic disorder briefly. We primarily included longitudinal studies published since 2009.

Controlling for depression in studies of anxiety and CVD outcomes

In a meta-analysis conducted by Roest et al. (2010), the presence of an anxiety disorder was found to increase the risk for both incident CHD (HR = 1.26; 95% CI: 1.15–1.38) and cardiac mortality (HR = 1.48; 95% CI: 1.14–1.92). While these results imply an association between anxiety and a subclass of CVD, namely CHD, it must be noted that only a very small amount of the studies included in this meta-analysis controlled for depression. This is problematic since the two disorders often co-occur and show similar symptoms that can be difficult to differentiate (Jacobson and Newman, 2017). Results comparable to the aforementioned meta-analysis have been reported by Emdin et al. (2016), although it should be noted that the latter study also lacks the inclusion of depression as a control. An indication of how vital it is to account for depression is evident in the meta-analysis by Celano et al. (2015), which included 32 studies, of which only 13 controlled for depression. While the authors did find a significant non-adjusted association of anxiety and mortality in patients with CHD, the role of depression might have attenuated this relation. When they included only the 13 studies accounting for depression as a covariate in a sensitivity analysis, they found no remaining significant association between anxiety and mortality. Tully et al. (2015) found an increased risk of CHD in people with panic disorder, a sub-diagnosis of anxiety in their meta-analysis. This effect persisted in studies that excluded cases of depression and in studies that adjusted for depression. Two meta-analyses have examined the relationship between anxiety and cerebrovascular disease (CER; Batelaan et al., 2016; Pérez-Piñar et al., 2017). Both identified a significant increase in risk of CER, though neither controlled for the effect of depression. Key characteristics of the discussed meta-analyses are presented in Table 1. Recent research has increasingly taken into consideration the importance of accounting for co-occurring depression when investigating the link between anxiety and CVD. For example, a meta-analysis by Batelaan et al. (2016) including 14 studies controlling for or removing cases of depression reports an association between anxiety and an increased risk for incident CVD (HR = 1.57, 95% CI 1.29–1.90). In a large retrospective cohort study by Liu et al. (2019) including 32,345 US-participants initially free of CHD, a significant association between Generalised Anxiety Disorder (GAD) and CHD was found (RR = 2.09; 95% CI: 1.22–3.58). A prognostic cohort study also conducted in the USA amongst 2041 initially CVD-free primary care patients yielded similar results: Patients who screened positive for anxiety at baseline had an elevated risk of a CVD event up to 3 years after baseline evaluation (Stewart et al., 2016). As this sample consisted predominantly of older and socioeconomically disadvantaged individuals, it remains unclear if the findings of Stewart and colleagues can be applied to the general US-population. The authors, however, stress the importance of the inclusion of usually under-represented groups.

Some studies, on the other hand, report no significant association between anxiety and CVD in initially CVD-free cohorts. In a prognostic cohort study including 853 Greek adults, Kyrou et al. (2017) reported an elevated adjusted risk of a CVD event for depression (OR = 3.6, 95% CI: 1.3–11) while there was no stable effect of anxiety (OR = 1.03, 95% CI: 1.0–1.1). In a study of 3135 elderly American men, anxiety was unrelated to either CHD or cerebrovascular disease (Karlsen et al., 2020). The analyses were adjusted for the effect of depression, and there was no effect of anxiety in either the group with a prior history of CVD or the group with no prior history.

Prognostic approaches to anxiety and CVD

A number of studies have applied a prognostic approach, i.e. focused on the association between anxiety and CVD in individuals who have previously experienced CVD events in their lifetime. These studies present similarly heterogeneous results as the CVD-free cohorts described above, not least owing to the high variety in sample characteristics. One of them, a study (AbuRuz et al., 2018) investigating the association of anxiety with Acute Myocardial Infarction (AMI) in Jordanian CHD-patients, reports a significantly elevated risk of an AMI-event for anxious CHD-patients (OR = 1.55; 95% CI: 1.15–2.10). However, several studies did not find such an association in other post-CVD samples with a more general CVD outcome. Nakamura et al. (2013) observed a significant association of depression, but not anxiety, with cardiovascular hospitalisation or death. Further, in a Danish cohort of 610 CHD patients, Versteeg et al. (2013) did not find a significant association between anxiety and cardiovascular hospitalisation or death, while depression was independently associated with both outcomes.

Adding to the complexity, study populations have included patients suffering from a variety of different diseases at baseline. Bruce et al. (2016) report an elevated risk of cardiovascular mortality, but not of incident CHD, for type 2 diabetes patients with GAD. In a Spanish study, anxiety was not significantly associated with an adverse cardiovascular event or mortality in a sample with metabolic syndrome (Ortega et al., 2018). Surveying a sample of female breast cancer survivors free of CVD in the Netherlands, Schoormans et al. (2017) found a significant association of pharmaceutically treated anxiety and CVD.

Conflicting findings

Some studies have found increased CVD risks from certain sub-diagnosis of anxiety, but not from others. Studies that have included generalised anxiety disorder as well as other sub-diagnosis of anxiety have found increased CVD risks of panic disorder, but not of generalised anxiety disorder (Seldenrijk et al., 2015; Tully and Baune, 2014). Aside from being addressed as a potential risk factor, anxiety has even been suggested as a cardio-protective factor in the context of CVD. Langvik and Nordahl (2014) found that anxiety reduced the risk of AMI in a large, longitudinal population survey, when controlling for depression. In a cross-sectional study by Huang et al. (2009) on the population of Taiwan, participants with an anxiety disorder, but no depression had a higher risk of having comorbid CHD or hypertension compared to healthy controls. The risk was greater for the younger age groups (<45 years) and reversed for those older than 64 years. Hence, older participants with anxiety were less at risk of having CHD or hypertension than healthy controls in the same age-group. In a study by Parker et al. (2011), the presence of Generalised Anxiety Disorder (GAD) in patients with acute coronary syndrome (ACS) significantly improved cardiac outcome, defined as a hard CVD event (for baseline GAD: OR = 0.35; 95% CI: 0.17–0.75; for lifetime GAD: OR = 0.42; 95% CI: 0.23–0.78). Key characteristics of the aforementioned single studies can be found in Table 2. This effect was, however, limited to patients suffering from GAD only and did not appear in conjunction with other anxiety disorders. A possible explanation offered by the authors is that GAD-patients might be more likely to seek medical assistance when experiencing somatic symptoms possibly stemming from their previous cardiac event. Additionally, greater adherence to therapy options and professional advice are also listed as plausible explanations (cf. Benyamini et al., 2013).

Possible underlying pathways

With regards to the possible mechanisms linking anxiety to increased CVD-risk or worse CVD-outcomes in CV-patients, there are two main suggested pathways: A behavioural pathway and a biological pathway (Cohen et al., 2015; Pan et al., 2017).

On the behavioural level, quite similarly to depression, anxious individuals may adhere to poorer health behaviour, which subsequently increases their CVD-risk (Cohen et al., 2015). Examples of such behaviour are lower physical activity, cigarette smoking, excessive alcohol consumption and poor diet. While non-adherence to medication is an example of poor health behaviour well documented for depression (Benyamini et al., 2013; DiMatteo et al., 2000), its occurrence in anxiety seems to be a matter of debate (cf. Cohen et al., 2015).

From a biological perspective, anxiety, like other negative emotions and chronic stress, is assumed to alter autonomic nervous system function via excessive activation of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system (Cohen et al., 2015). This, in turn, causes endothelial damage due to an increased release of plasma catecholamines, which ultimately leads to the development of CVD, such as atherosclerosis, CAD and acute coronary events. The understanding of these mechanisms has been expanded on in recent years by evidence linking atherosclerosis to chronic inflammation, and not, as was the previous consensus, to a mere accumulation of cholesterol (Fioranelli et al., 2018). While an association has been established between depression and inflammatory markers (Kop et al., 2010), the relation between anxiety and inflammation is still inconclusive (Celano et al., 2018). In the case of a more concrete definition of an anxiety disorder however, namely GAD, results seem to indicate an association with inflammation markers in CHD-patients (Bankier et al., 2008).

Table 2. Key characteristics of discussed single-studies.

Study	*N*	Sample (country)	Mean age (SD/range)
AbuRuz et al. (2018)	1000	CHD patients (Jordan)	66.6 (11.1)
Bruce et al. (2016)	1337	Type 2 diabetes (Australia)	64.9 (14.4)
Huang et al. (2009)	1,031,557	Whole population (Taiwan)	Four groups: <20, 20–44, 45–64, 65⩽. No information on distribution
Karlsen et al. (2020)	3095	Community sample (US)	76.4 (5.5)
Kyrou et al. (2017)	853	CVD-free (Greece)	F: 44 (18), M: 45 (13)
Langvik and Nordahl (2014)	41,248	CHD-free (Norway)	Non-MI: F: 43.12 (13.07), M: 43.61 (12.90), MI: F: 57.87 (9.31), M: 55.81 (9.44)
Liu et al. (2019)	32,345	CHD-free (US)	45.3 (17.2)
Nakamura et al. (2013)	414	CVD (Japan)	64.9 (13.1)
Ortega et al. (2018)	401,743	MetS (Spain)	60.11 (9.9)
Parker et al. (2011)	489	ACS (Australia)	65.7 (12.2)
Schoormans et al. (2017)	7227	CVD-free breast cancer survivors (Netherlands)	CVD: 70 (46–91); No CVD: 60 (23–102)
Seldenrijk et al. (2015)	2510	CVD-free (Netherlands)	41.2 (18–65)
Stewart et al. (2016)	2041	CVD-free primary care patients (US)	68.5 (6.9)
Tully and Baune (2014)	4181	Stratified sample (Germany)	43.5 (SD 11.6, range 18–65)
Versteeg et al. (2013)	610	CHD-patients (Denmark)	65.8 (10.8)

Sex	Follow-up (years)	Anxiety type (measure)	Outcome	Results (95% CI)
M + F	2	Anxiety (HADS)	MI	OR = 1.55 [1.15, 2.10]
M + F	4	GAD (GADS)	All-cause mortality + CV-mortality + incident CHD	CVMort: HR = 4.60 [1.62, 13.08], CHD: HR = 1.26 [0.67, 2.36]
M + F	0 (cross-sectional)	Anxiety disorders (diagnosis)	CHD	Average RR for age groups: <20 = 9.88, 20–44 = 3.86, 45–64 = 1.4, 65⩽ = 0.66
M	12	GAD (GADS)	CHD + CER	CHD HR = 0.95 [0.71, 1.27], CER HR = 1.33 [0.69, 1.77]
M + F	10	Anxiety (STAI-state anxiety subscale)	CVD	OR = 1.03 [1.0, 1.1]
M + F	7.2	Anxiety (HADS)	MI	OR = 0.61 [0.50, 0.79]
M +	F 3	Anxiety disorders (AUDADIS-IV + psychiatric diagnoses)	Incident CHD	RR = 2.09 [1.22, 3.58]
M + F	1.18	Anxiety disorders (GAD-7)	CV-hospitalisation or death	HR = 2.35 [0.77, 6.18]
M + F	4.91	Anxiety disorder diagnosis (Health databank)	Incident CV-events + mortality	RR = 0.99 [0.95, 1.02]
M + F	5	Anxiety disorders (CIDI + research assistant's verdict + HADS-A)	Cardiac admission/death/event	GAD: 5-year OR = 0.35 [0.17, 0.75], lifetime OR = 0.42 [0.23, 0.78]
F	13	Anxiety (Drug dispenses for anxiety disorders)	CVD (at least two drug dispenses)	HR = 1.48 [1.05, 2.08]
M + F	5.5	Generalised anxiety disorders, panic disorder (DSM-IV, CIDI)	CVD	GAD: adjusted RR = 1.28 [0.71, 2.30], Panic disorder: adjusted RR = 2.12 [1.27, 3.55]
M + F	8	Anxiety (Prime-MD)	Hard CVD event (fatal/acute MI, stroke)	HR = 1.53 [1.20, 1.95] within 0–3 years of follow-up
M + F	0 (12-month prevalence)	Generalised anxiety disorders, panic disorder (DSM-IV, CIDI)	CVD	GAD: adjusted OR = 0.94 [0.37, 2.37], Panic disorder: adjusted OR = 2.89 [1.47, 5.69]
M + F	5	Anxiety (HADS)	Cardiac-related hospitalisation or all-cause mortality	HR = 0.96 [0.70, 1.32] for first hospitalisation

CHD: coronary heart disease; HADS: Hospital Anxiety and Depression Scale; MI: myocardial infarction; GAD: generalised anxiety disorder; GADS: Generalised Anxiety Disorder Scale; CV: cardiovascular; STAI: state-trait anxiety inventory; AUDADIS: the alcohol use disorder and associated disabilities interview schedule; GAD-7: Generalised Anxiety Disorder 7-item Scale; MetS: metabolic syndrome; ACS: acute coronary syndrome; CIDI: composite international diagnostic interview; Prime-MD: primary care evaluation of mental disorders.

Discussion

Research addressing anxiety as a risk factor for CVD often presents itself as a challenging mosaic of varying definitions, measures and sample characteristics. This is to be expected, as the term CVD implies a very broad range of diseases and definitions. However, as the differing practices observed in many studies pose a hindrance to further understanding of a potentially very relevant association, we make several suggestions that are aimed at helping to determine the real association between anxiety and CVD:

Firstly, there exists considerable variety regarding sample characteristics, with some samples consisting of participants free of CVD, while the majority of studies investigates either CVD-samples or those with risk factors for CVD. More research on initially CVD-free samples representing the general population would make the interpretation of research results and the drawing of valid conclusions easier.

We have stated above the importance of any research on the association of anxiety with CVD to bear in mind the role of comorbid depression. While newly published studies do seem to control for depression more frequently, more studies should take this factor into consideration. It will be interesting to see if and how pooled results of meta-analyses change once more studies account for depression.

Furthermore, there is a lack of specificity in terms of measures utilised by researchers. While many authors choose to use screening measures for anxiety, the variance in screening questionnaires (see Table 2) often leads to quite different rates of detected anxiety across studies. Moreover, the use of cut-off criteria is often opaque, that is, it is unclear whether anxious participants are compared to an anxiety-free, or merely a lower-scoring, group. Davidson et al. (2005) discuss some of these challenges in relation to depression, and it is likely that these arguments are applicable to anxiety as well. We therefore suggest to either use clinical diagnoses in order to categorise participants into groups with or without a defined anxiety disorder, or to employ a valid screening measure and use its continuous anxiety scale or a cut-off that differentiates solid cases of anxiety from cases of no anxiety. Similarly, studies are not always specific in their measurement of the construct anxiety. As different sub-diagnoses of anxiety (GAD, panic disorder, phobias) can have a different impact on CVD risk, this should be considered by researchers. In the same vein, while some studies examine CHD or CER, or AMI and stroke specifically, others examine the broader category of CVD in general. A lack of specificity may obscure potential relationships that exist at the sub-categories of CVD. Although some researchers (cf. Batelaan et al., 2016) found that the effect of anxiety was not different across CVD subcategories, we would still recommend that researchers run separate analyses for CHD and CER outcomes.

Limitations

A narrative review like this study falls short in comparison with a systematic review that would have increased the likelihood of including all relevant new findings. Narrative reviews are criticised for lacking the synthesis and rigour of a systematic review, but have the advantage of being broader in scope than systematic reviews (Byrne, 2016). Likewise, it would have been beneficial to follow the PRISMA checklist (Moher et al., 2009), to comply with the standard of a systematic review, for example, focusing more in detail on synthesis of the results and risk of bias. Further, firm conclusions about the role of anxiety as a risk factor of CVD awaits rigorous meta-analysis. As we only used English terms in our searches, any potential new findings published in a non-English language would not be discovered and included in our review.

Conclusion and practical implications

In this paper, we have reviewed the current empirical status of anxiety as a risk factor for CVD independent of depression. It is evident that there still is substantial uncertainty about the status of anxiety as an independent risk marker for both incident and recurrent CVD. In our opinion, further research into this should take care to be population specific, measurement specific and outcome specific to elucidate this. Despite obvious limitations associated with narrative reviews, the results suggest that the current standing of anxiety as an independent risk marker of CVD is 'possible', and should not be treated interchangeable with depression, despite their co-morbidity. Hence, international guidelines for CVD prevention (e.g. Piepoli et al., 2016) should be revised accordingly pending sufficient empirical evidence and scrutinised investigation allowing for firm conclusions. Further, when targeting mental health to reduce the risk of CVD, treating depression should be prioritised.

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Paper III

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Paper IV

Sex-specific psychological risk profiles of CVD in the HUNT study: The role of neuroticism and extraversion *

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Abstract

Objective: The aim was to investigate psychological risk profiles of cardiovascular disease (CVD). Depression and anxiety have been linked to CVD, but less research exists on the role of personality. Previous studies warrant sex-specific analyses. In this study we examine the role of sex, neuroticism, extraversion, anxiety and depression on the risk of CVD.

Method: Using data from the HUNT-study and the mortality register, 32 383 (57.10% men) participants were followed for an average of 10.48 years. During this time, 142 died of myocardial infarction (MI) and 111 of stroke.

Results: Sex-specific Cox regression analyses showed that extraversion predicted stroke for women, while neuroticism predicted MI for men.

Conclusion: Personality appear to have sex-specific effect on MI and stroke.

Keywords: *Psychocardiology, personality, depression, anxiety, myocardial infarction, stroke, extraversion, neuroticism*

Introduction

Ischaemic heart disease (CHD) and stroke are leading causes of death globally (Wang et al., 2016). According to guidelines (Visseren et al., 2021), persons with mental disorders are subject to special attention when it comes to prevention of cardiovascular disorders (CVD). Anxiety and depression are related to CVD (Gan et al., 2014; Wu & Kling, 2016), though depression more strongly than anxiety (Karlsen et al., 2021). Both angry and sadness rumination can

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cause cardiovascular reactivity in terms of increased heart rate and blood pressure (Busch et al., 2017). On the other hand, metabolic and inflammatory factors (i.e., diabetes, triglycerides and waist circumference and C-reactive protein) are prospectively associated with the onset of depression (Rudaz et al., 2017), and more evidence is needed on the role of psychosocial factors and whether they improve risk prediction beyond traditional risk factors (Visseren et al., 2021). While anxiety and depression are distinct mental disorders, they have overlapping symptomology and are frequently comorbid (Brown et al., 2001; Jacobson & Newman, 2017). They also share neurobiological correlates (Neumann, 2020). Both anxiety and depression are closely linked to dispositional tendencies to experience negative emotions, i.e., the personality trait neuroticism (Kotov et al., 2010). Meta-analysis supports the prospective association between neuroticism and mental disorders (Jeronimus et al., 2016). The health impairment associated with the trait makes the economic cost of neuroticism substantial (Cuijpers et al., 2010). Symptoms of depression and anxiety often present trait-like properties in the general populations (Langvik & Hjemdal, 2015) implying that the role of dispositional factors when investigating depression should be considered. For an overview of the various models proposed for the link between neuroticism and common mental disorders, see Ormel et al. (2013). A recent study addresses the importance of incorporating neuroticism when examining the role of mental health and CVD, focusing on the joint contribution of different aspects of mental health (Li et al., 2021).

While neuroticism represents a vulnerability to developing affective disorders in general, the trait extraversion is especially related to depression (Watson et al., 2015). The core of extraversion is sociability and positive emotions (McCrae & Costa, 2010). Positive affect has been identified as protective against 10-year incident coronary heart disease, also when controlling for depression (Davidson et al., 2010). Hence, personality has relevance for CVD risk not only as a predictive factor of affective disorders, and the role of personality as a risk factor for CVD have been investigated for several decades (Denollet et al., 1996; Friedman, 1959; Jokela et al., 2014).

Personality traits influence both frequency and intensity of positive and negative emotions (Komulainen et al., 2014), and while personality traits describe dimensional aspects of personality, the *typology* approach focuses on distinct categories, like the Type A personality typology characterized by e.g. aggressiveness (Friedman, 1959). Despite its popularity in popular psychology, a large-scale study applying different measures of Type A assessment, concluded that there is no evidence to support the Type A as a CVD risk factor (Šmigelskas et al., 2014). Another personality construct that has received attention is the Type D personality, defined by a combination of negative affectivity and social inhibition (Denollet & Brutsaert, 1998). Much research exists on the increased mortality of CVD patients with type D personality (Denollet & Brutsaert, 1998; de Voogd et al., 2012; Grande et al., 2012; Kupper & Denollet, 2018). A review of the prognostic value of Type D in cardiac samples

concluded that the effect sizes probably have been overestimated (Grande et al., 2012), and the research has been criticised for lacking statistical power and wrongly dichotomising Type D personality instead of treating it like a continuous trait (Coyne et al., 2011). As an etiologic factor, Type D has received less attention, although one study failed to identify association between Type D and incident CHD (Larson et al., 2012). However, the sub-component of Type D, namely social inhibition has been associated with coronary artery plaque in CHD-free populations (Compare et al., 2014). The Type D sub-scales of social inhibition and negative affect are strongly correlated to extraversion, neuroticism, conscientiousness, agreeableness and openness traits from the five-factor model (De Fruyt & Denollet, 2002). Although different taxonomies on personality have been given attention over the years, the majority of personality constructs likewise correspond to the factors in the five-factor model (McCrae, 2010; McCrae & John, 1992), and more recent biological approach to personality emphasis the possible integration of different models, where extraversion and neuroticism represent an alpha and beta factor (Markon et al., 2005).

Although neuroticism predicts all-cause mortality (O'Súilleabháin & Hughes, 2018) and is linked to immune functioning (Mengelkoch et al., 2022), and extraversion is suggested as a predictor of longevity (Chapman et al., 2011), several questions remains whether neuroticism and extraversion is associated with CVD or CVD mortality (Otonari et al., 2021). Studies have observed that neuroticism is related to higher risk of death from cardiovascular disease (Shipley et al., 2007), and some that neuroticism has a link to CVD independent of depression (Čukić & Bates, 2015). Other studies suggest that that neuroticism has a synergistic interaction with depression, increasing CVD risk (Almas et al., 2017).

Jokela et al. (2014) found that extraversion was linked to increased risk of stroke mortality, while neuroticism was linked to increased risk of CHD mortality. However, a large prospective cohort study from Japan found no relationship between CVD mortality and either extraversion or neuroticism on CVD (Narita et al., 2020), addressing the need for more research on the link between personality and CVD.

Sex and gender differences in associations between personality and CVD

Research done on women and psychological risk factors of CVD is scarce (Espnes et al., 2015), and studies of women have been underpowered compared to those of men (Visseren et al., 2021). The lifetime prevalence and morbidity of depressive disorders are higher in females than in males (Faravelli et al., 2013; Piccinelli & Wilkinson, 2000). Gender differences in personality traits are considered small but consistent across cultures (Costa et al., 2001), women tend to score higher on neuroticism compared to men, whereas for extraversion, women scored higher on the extraversion facets of warmth, gregariousness and

positive emotions. However, some argue that the gender differences in personality are substantial, and that a use of multivariate approach offers a different perspective on sex differences (Kaiser et al., 2019).

Biological sex influence CVD risk through sex-specific and unique risk factors like pregnancy or polycystic ovaries syndrome (Cho et al., 2020). Sex hormones affect neurotransmitters like serotonin and dopamine (Barth et al., 2015), and studies has identified that the personality-psychopathology connection is moderated by sex (Neumann, 2020).

Gender, which refers to the socially constructed roles, behavior, expressions, and identities of individuals, is also an important aspect to consider when investigating sex differences in CVD (Connelly et al., 2021). Large-scale studies have identified and that there is a gender-specific association between depression and CVD (Haukkala et al., 2009), and both anxiety, depression and stress are important factors to consider in CVD prevention for women (Cho et al., 2020). A study found that neuroticism increased the risk of CVD mortality in women with low socio-economic status (SES) but lowered the risk for women with high SES (Hagger-Johnson et al., 2012), suggesting that societal factors play an important role. For cancer mortality, the effect of personality is opposite for men and women (Otonari et al., 2021). Further, studies have shown that associations between personality and different cardiovascular outcome differ between men and women (Jokela et al., 2014), and that the associations between mental health and risk of CVD is stronger among females than men (Li et al., 2021), suggesting that research should be both gender and outcome specific.

Summary and research aim

Studies on personality and CVD that report no association between the two often use CVD as a general outcome combining both myocardial infarction and stroke (Almas et al., 2017; Hagger-Johnson et al., 2012). However, research suggest that the association between personality and CVD depends on both outcome and gender (Jokela et al., 2014). Given the role of personality as a predictor of affective disorders and stress (Kotov et al., 2010; Ormel et al., 2013), gender differences in personality (Costa et al., 2001; Kaiser et al., 2019) and affective disorders (Faravelli et al., 2013; Neumann, 2020; Piccinelli & Wilkinson, 2000), including the gender-specific association between psychological variables and CVD outcomes (Hagger-Johnson et al., 2012; Haukkala et al., 2009; Jokela et al., 2014; Li et al., 2021), it is pivotal to address the role of personality as a predictor for different CVD outcomes. In this study, we investigate the role of the personality traits neuroticism and extraversion as predictors for stroke and MI separately for men and women, controlling for anxiety and depression.

Methods

Participants

This study uses data collected for The Trøndelag Health Study (HUNT). All participants in the Nord-Trøndelag area of Norway were invited to participate in a longitudinal population study in 1984. Every decade since, those same participants, as well as people who have moved to that area since, have been invited to participate again. The current study uses data from the third wave of data collection (2006-2008). This data was combined with data from the Norwegian Cause of Death Registry to identify deaths related to stroke and MI. Participants with missing data on any of the variables included in the statistical models were excluded. This left a total sample of 32 383 participants. The average age of participants at the time of the study start was 52.25 (SD = 14.18). There were more women than men in the sample, at 57.10 percent (n = 18 490). Further information about HUNT can be found in Holmen et al. (2003) and Krokstad et al. (2013).

Measures

Cardiovascular disease. The DÅR records the cause of death for each person who either dies in Norway or is registered as living in Norway. The cause of death is determined by a physician and follows the ICD-10 system for classifying diseases and health problems. In this study, ICD-10 codes I21 to I22 indicated death by MI, while ICD-10 codes I60 to I69 indicated death by stroke.

Personality. Extraversion and neuroticism were measured using a questionnaire based on the Revised Eysenck Personality Questionnaire (Eysenck et al., 1985). The items were translated based on the Norwegian version of the standard Eysenck Personality Questionnaire (Eysenck & Tambs, 1990). Extraversion and neuroticism were both measured using six items.

Symptoms of anxiety and depression. Anxiety and depression were measured as a continuous variable, using the Hospital Anxiety and Depression Scales (Zigmond & Snaith, 1983). A Norwegian translation was made specifically for the HUNT study (HUNT, 2021).

Covariates. We added common risk factors of CVD to the statistical models: systolic blood pressure, cholesterol level, waist-hip ratio, age, sex, diabetes, smoking status and antidepressant use.

Systolic blood pressure. Systolic blood pressure was measured by trained nurses using oscillometry. The participants had been seated for two minutes before measurements were taken. Three measurements were recorded, and the mean of the second and third was used.

Waist-hip ratio. Measurements of the waist and hip were taken with a steel band while participants were standing. The hip circumference was measured at the thickest part, while the waist was measured at the height of the umbilicus.

Cholesterol. Serum cholesterol was analysed by enzymatic cholesterol esterase methodology.

Additionally, sex and age were recorded. The presence of diabetes and smoking status was self-reported via questionnaires.

Statistical analysis

We analysed cox proportional hazards model to analyse the survival data. We ran two analyses: one with fatal myocardial infarction as the outcome, the other with fatal stroke as the outcome. For each of these conditions we first analysed the whole sample, then ran separate analyses for men and women. R v.3.6.3 with the survival package v.3.2-12 was used for the analyses. For each model, Royston and Sauerbrei's pseudo-R^2 was reported (Royston & Sauerbrei, 2004), alongside the Wald test, the LR test and the Log Likelihood.

Results

Descriptive statistics and group differences are displayed in Table 1. The average time to endpoint (fatal MI or stroke, or censored) was 10.48 years, during which 142 participants died of MI while 111 died of stroke.

The results of the cox regression analyses using the whole sample are displayed in Table 2. Simple effects are the effects of the variable alone without any other variable in the regression model. Model 1 includes only extraversion and neuroticism, while Model 2 includes extraversion, neuroticism, symptoms of depression and symptoms of anxiety in addition. Model 3 includes all the of the variables and all relevant covariates.

In the total sample, extraversion significantly reduced the risk of myocardial infarction (MI) in Model 1. When including neuroticism, depression and anxiety symptoms in Model 2, its effect was no longer significant. Neuroticism and depression significantly increased the risk of MI, while anxiety significantly decreased it. In the final model with all covariates, neuroticism and depression significantly increased the risk of MI. When looking only at women (Table 3), the pattern was similar for Model 2. However, no variables apart from age and current smoking had a significant impact on the risk of MI in the final model. When looking at men only (Table 4), neither extraversion nor neuroticism had a significant simple effect. Neither did they have an effect in Model 1. In Model 2, however, neuroticism and depression significantly increased the risk of MI, while anxiety decreased it. In the final Model 3, neuroticism was the only one of these variables that significantly impacted MI, increasing the risk.

When looking at the simple effects, extraversion significantly reduced the risk of stroke, while neuroticism and depression significantly increased the risk of stroke, in the total sample (Table 2). Only extraversion had a significant impact in Model 1, though this disappeared in Model 2 where depression significantly increased the risk of stroke, while anxiety significantly decreased it.

Table 1. Descriptive statistics for those who had MI or stroke vs. those who did not, for the total sample, women and men respectively.

	Total			Women			Men		
	No MI (*N* = 32241)	MI (*N* = 142)	*p*	No MI (*N* = 18435)	MI (*N* = 55)	*p*	No MI (N = 13806)	MI (*N* = 87)	*p*
Extraversion	3.69 (1.79)	3.24 (1.68)	.003	3.78 (1.76)	3.20 (1.54)	.015	3.57 (1.82)	3.26 (1.77)	.118
Neuroticism	1.63 (1.71)	1.96 (1.78)	.022	1.89 (1.77)	2.55 (1.83)	.006	1.28 (1.55)	1.59 (1.65)	.067
Depression	3.19 (2.84)	4.54 (2.96)	< .001	3.02 (2.81)	4.82 (2.87)	< .001	3.42 (2.86)	4.37 (3.02)	.002
Anxiety	3.99 (3.27)	3.82 (3.16)	.544	4.33 (3.44)	4.76 (3.39)	.354	3.54 (2.98)	3.23 (2.87)	.340
SBP	130.12 (18.25)	144.68 (23.53)	< .001	127.38 (18.93)	146.36 (25.10)	< .001	133.79 (16.62)	143.62 (22.56)	< .001
Cholesterol	5.55 (1.08)	5.99 (1.01)	< .001	5.58 (1.12)	6.16 (1.16)	< .001	5.52 (1.04)	5.88 (0.89)	.001
WHR	0.90 (0.08)	0.94 (0.07)	< .001	0.87 (0.07)	0.91 (0.07)	< .001	0.94 (0.06)	0.97 (0.06)	< .001
Age	52.16 (14.78)	72.16 (10.38)	< .001	51.57 (15.12)	75.01 (11.12)	< .001	52.95 (14.28)	70.36 (9.51)	< .001
Diabetes									
No	31039 (96.3%)	126 (88.7%)	< .001	17824 (96.7%)	49 (89.1%)	.002	13215 (95.7%)	77 (88.5%)	< .001
Yes	1202 (3.7%)	16 (11.3%)		611 (3.3%)	6 (10.9%)		591 (4.3%)	10 (11.5%)	
Smoking									
Never	14169 (43.9%)	51 (35.9%)	.062	8243 (44.7%)	27 (49.1%)	.531	5926 (42.9%)	24 (27.6%)	.004
Former	10428 (32.3%)	51 (35.9%)		5583 (30.3%)	16 (29.1%)		4845 (35.1%)	35 (40.2%)	
Sometimes	2295 (7.1%)	7 (4.9%)		1206 (6.5%)	1 (1.8%)		1089 (7.9%)	6 (6.9%)	
Current	5349 (16.6%)	33 (23.2%)		3403 (18.5%)	11 (20.0%)		1946 (14.1%)	22 (25.3%)	
Stroke									
No stroke	32130 (99.7%)	142 (100.0%)	.484	18367 (99.6%)	55 (100.0%)	.652	13763 (99.7%)	87 (100.0%)	.602
Stroke	111 (0.3%)	0 (0.0%)		68 (0.4%)	0 (0.0%)		43 (0.3%)	0 (0.0%)	
Sex									
Female	18435 (57.2%)	55 (38.7%)	< .001						
Male	13806 (42.8%)	87 (61.3%)							

Table 1 continued.

	Total			Women			Men		
	No stroke (*N* = 32272)	Stroke (*N* = 111)	*p*	No stroke (*N* = 18422)	Stroke (*N* = 68)	*p*	No stroke (N = 13850)	Stroke (*N* = 43)	*p*
Extraversion	3.69 (1.79)	3.17 (1.70)	.002	3.78 (1.76)	3.50 (1.56)	.192	3.57 (1.82)	2.65 (1.81)	< .001
Neuroticism	1.63 (1.71)	1.97 (1.77)	.034	1.89 (1.77)	2.38 (1.84)	.022	1.28 (1.55)	1.33 (1.44)	.859
Depression	3.19 (2.84)	4.53 (3.21)	< .001	3.02 (2.81)	4.49 (3.36)	< .001	3.43 (2.86)	4.60 (3.01)	.007
Anxiety	3.99 (3.27)	4.23 (3.62)	.432	4.33 (3.44)	4.63 (3.91)	.473	3.53 (2.98)	3.60 (3.03)	.875
SBP	130.14 (18.27)	145.57 (22.01)	< .001	127.37 (18.92)	145.25 (24.89)	< .001	133.81 (16.66)	146.07 (16.73)	< .001
Cholesterol	5.55 (1.08)	5.90 (1.20)	< .001	5.58 (1.12)	6.13 (1.25)	< .001	5.52 (1.04)	5.54 (1.04)	.927
WHR	0.90 (0.08)	0.93 (0.08)	< .001	0.87 (0.07)	0.90 (0.08)	< .001	0.94 (0.06)	0.97 (0.06)	< .001
Age	52.17 (14.78)	74.67 (9.93)	< .001	51.55 (15.10)	76.52 (9.48)	< .001	53.00 (14.30)	71.75 (10.03)	< .001
Diabetes									
No	31063 (96.3%)	102 (91.9%)	.016	17810 (96.7%)	63 (92.6%)	.065	13253 (95.7%)	39 (90.7%)	.108
Yes	1209 (3.7%)	9 (8.1%)		612 (3.3%)	5 (7.4%)		597 (4.3%)	4 (9.3%)	
Smoking									
Never	14167 (43.9%)	53 (47.7%)	.326	8230 (44.7%)	40 (58.8%)	.077	5937 (42.9%)	13 (30.2%)	.225
Former	10442 (32.4%)	37 (33.3%)		5582 (30.3%)	17 (25.0%)		4860 (35.1%)	20 (46.5%)	
Sometimes	2299 (7.1%)	3 (2.7%)		1206 (6.5%)	1 (1.5%)		1093 (7.9%)	2 (4.7%)	
Current	5364 (16.6%)	18 (16.2%)		3404 (18.5%)	10 (14.7%)		1960 (14.2%)	8 (18.6%)	
MI									
No MI	32130 (99.6%)	111 (100.0%)	.484	18367 (99.7%)	68 (100.0%)	.652	13763 (99.4%)	43 (100.0%)	.602
MI	142 (0.4%)	0 (0.0%)		55 (0.3%)	0 (0.0%)		87 (0.6%)	0 (0.0%)	
Sex									
Female	18422 (57.1%)	68 (61.3%)	.375						
Male	13850 (42.9%)	43 (38.7%)							

Note. SBP = systolic blood pressure. WHR = waist hip ratio. MI = myocardial infarction. For continuous measures, mean and standard deviations are shown. For categorical measures, frequency and percentage are shown.

Table 2. Hazard ratios of neuroticism, extraversion, depression and anxiety on risk of CVD mortality. (N = 32,383)

	Myocardial infarction			
	Simple effects	Model 1	Model 2	Model 3
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Extraversion	0.87** (0.80, 0.95)	0.88** (0.81, 0.97)	0.96 (0.87, 1.05)	1.07 (0.97, 1.19)
Neuroticism	1.11* (1.02, 1.22)	1.09 (0.99, 1.19)	1.19** (1.05, 1.36)	1.23** (1.08, 1.40)
Depression	1.15*** (1.09, 1.20)		1.20*** (1.13, 1.28)	1.07* (1.00, 1.14)
Anxiety	0.98 (0.93, 1.04)		0.83*** (0.77, 0.90)	0.93 (0.86, 1.00)
Diabetes				1.61 (0.94, 2.75)
SBP				1.01* (1.00, 1.02)
Cholesterol				1.25** (1.07, 1.45)
WHR				16.63* (1.53, 181.14)
Smoking				
Former				0.95 (0.63, 1.42)
Sometimes				1.11 (0.50, 2.47)
Current				2.35*** (1.49, 3.71)
Age				1.13*** (1.11, 1.15)
Sex				2.30*** (1.54, 3.44)
R^2_D		0.05	0.19	0.66
Log Likelihood		-1457.16	-1435.75	-1263.15
Wald Test		12.68** (df = 2)	62.67*** (df = 4)	295.83*** (df = 13)
LR Test		12.34** (df = 2)	55.16*** (df = 4)	400.34*** (df = 13)
Logrank Test		12.83** (df = 2)	62.32*** (df = 4)	343.55*** (df = 13)
	Stroke			
	Simple effects	Model 1	Model 2	Model 3
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Extraversion	0.85** (0.77, 0.94)	0.86** (0.78, 0.96)	0.93 (0.83, 1.03)	1.05 (0.93, 1.18)
Neuroticism	1.12* (1.01, 1.24)	1.09 (0.98, 1.21)	1.10 (0.95, 1.28)	1.06 (0.91, 1.24)
Depression	1.15*** (1.09, 1.21)		1.17*** (1.09, 1.25)	1.06 (0.99, 1.14)
Anxiety	1.02 (0.97, 1.08)		0.90* (0.83, 0.98)	1.01 (0.93, 1.10)
Diabetes				1.02 (0.51, 2.05)
SBP				1.01 (1.00, 1.02)
Cholesterol				1.03 (0.86, 1.22)
WHR				8.84 (0.63, 124.73)
Smoking				
Former				0.90 (0.58, 1.40)
Sometimes				0.58 (0.18, 1.87)
Current				1.66 (0.95, 2.91)
Age				1.16*** (1.14, 1.18)
Sex				0.91 (0.58, 1.44)
R^2_D		0.06	0.15	0.69
Log Likelihood		-1127.85	-1118.17	-957.66
Wald Test		12.29** (df = 2)	35.32*** (df = 4)	246.34*** (df = 13)
LR Test		11.98** (df = 2)	31.35*** (df = 4)	352.36*** (df = 13)
Logrank Test		12.47** (df = 2)	35.79*** (df = 4)	319.37*** (df = 13)

Note. *p < .05; **p < .01; ***p < .001. SBP = Systolic blood pressure. WHR = waist hip ratio. LR = Likelihood ratio. Model 1: Combined effects of personality traits. Model 2: Model 1 + effects of mood disorder symptoms. Model 3: Model 2 + all risk markers. Pseudo R^2 is calculated according to Royston and Sauerbrei (2004). Baseline for smoking is n*ever*, baseline for sex is *female*.

Table 3. Hazard ratios of personality, depression and anxiety on risk of CVD mortality among women (N = 18,490)

	Myocardial infarction			
	Simple effects	Model 1	Model 2	Model 3
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Extraversion	0.83* (0.72, 0.96)	0.86 (0.75, 1.00)	0.94 (0.81, 1.10)	1.09 (0.91, 1.29)
Neuroticism	1.21** (1.05, 1.39)	1.17* (1.02, 1.35)	1.23* (1.00, 1.50)	1.18 (0.96, 1.44)
Depression	1.19*** (1.10, 1.27)		1.22*** (1.11, 1.34)	1.10 (1.00, 1.22)
Anxiety	1.04 (0.96, 1.11)		0.86** (0.77, 0.96)	0.95 (0.85, 1.07)
Diabetes				1.48 (0.61, 3.58)
SBP				1.01 (1.00, 1.02)
Cholesterol				1.10 (0.86, 1.39)
WHR				11.26 (0.35, 365.88)
Smoking				
Former				1.29 (0.68, 2.43)
Sometimes				0.53 (0.07, 3.97)
Current				2.68* (1.25, 5.74)
Age				1.15*** (1.12, 1.19)
R^2_D		0.11	0.23	0.70
Log Likelihood		-530.92	-522.48	-443.59
Wald Test		11.26** (df = 2)	32.35*** (df = 4)	129.15*** (df = 12)
LR Test		10.82** (df = 2)	27.70*** (df = 4)	185.47*** (df = 12)
Logrank Test		11.54** (df = 2)	33.10*** (df = 4)	170.18*** (df = 12)
	Stroke			
	Simple effects	Model 1	Model 2	Model 3
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Extraversion	0.92 (0.80, 1.04)	0.94 (0.82, 1.08)	1.02 (0.89, 1.17)	1.21* (1.04, 1.42)
Neuroticism	1.16* (1.02, 1.31)	1.14* (1.01, 1.30)	1.18 (0.98, 1.41)	1.14 (0.95, 1.37)
Depression	1.16*** (1.08, 1.24)		1.21*** (1.11, 1.32)	1.09 (0.99, 1.19)
Anxiety	1.02 (0.96, 1.09)		0.87** (0.79, 0.96)	0.98 (0.89, 1.09)
Diabetes				0.95 (0.37, 2.42)
SBP				1.00 (0.99, 1.02)
Cholesterol				1.04 (0.84, 1.29)
WHR				4.11 (0.18, 94.01)
Smoking				
Former				0.95 (0.53, 1.70)
Sometimes				0.34 (0.05, 2.50)
Current				1.78 (0.84, 3.74)
Age				1.18*** (1.15, 1.21)
R^2_D		0.06	0.18	0.74
Log Likelihood		-651.13	-642.41	-526.28
Wald Test		6.13* (df = 2)	27.05*** (df = 4)	168.93*** (df = 12)
LR Test		5.89 (df = 2)	23.33*** (df = 4)	255.59*** (df = 12)
Logrank Test		6.22* (df = 2)	27.29*** (df = 4)	236.49*** (df = 12)

Note. *p < .05; **p < .01; ***p < .001. SBP = Systolic blood pressure. WHR = waist hip ratio. LR = Likelihood ratio. Model 1: Combined effects of personality traits. Model 2: Model 1 + effects of mood disorder symptoms. Model 3: Model 2 + all risk markers. Pseudo R^2 is calculated according to Royston and Sauerbrei (2004). Baseline for smoking is n*ever*.

Table 4. Hazard ratios of personality, depression and anxiety on risk of CVD mortality among men (*N* =13,893)

	Myocardial infarction			
	Simple effects	Model 1	Model 2	Model 3
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Extraversion	0.91 (0.81, 1.02)	0.92 (0.82, 1.04)	0.97 (0.86, 1.10)	1.06 (0.94, 1.21)
Neuroticism	1.12 (0.99, 1.27)	1.11 (0.98, 1.25)	1.27** (1.06, 1.51)	1.26** (1.06, 1.50)
Depression	1.11** (1.04, 1.18)		1.15*** (1.07, 1.25)	1.05 (0.96, 1.14)
Anxiety	0.96 (0.89, 1.04)		0.82*** (0.73, 0.91)	0.91 (0.82, 1.01)
Diabetes				1.73 (0.88, 3.41)
SBP				1.01 (1.00, 1.02)
Cholesterol				1.35** (1.10, 1.64)
WHR				20.20 (0.87, 469.40)
Smoking				
Former				0.84 (0.50, 1.43)
Sometimes				1.33 (0.54, 3.28)
Current				2.28** (1.27, 4.09)
Age				1.12*** (1.10, 1.15)
R^2_D		0.03	0.16	0.60
Log Likelihood		-819.73	-809.5	-721.56
Wald Test		5.31 (df = 2)	27.53*** (df = 4)	159.84*** (df = 12)
LR Test		5.08 (df = 2)	25.54*** (df = 4)	201.42*** (df = 12)
Logrank Test		5.36 (df = 2)	27.38*** (df = 4)	172.69*** (df = 12)
	Stroke			
	Simple effects	Model 1	Model 2	Model 3
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Extraversion	0.76** (0.64, 0.89)	0.75*** (0.64, 0.89)	0.80* (0.67, 0.95)	0.86 (0.72, 1.04)
Neuroticism	1.02 (0.84, 1.23)	0.97 (0.80, 1.17)	0.94 (0.72, 1.22)	0.94 (0.72, 1.23)
Depression	1.13** (1.04, 1.24)		1.14* (1.02, 1.27)	1.03 (0.91, 1.16)
Anxiety	1.01 (0.91, 1.11)		0.94 (0.82, 1.09)	1.07 (0.93, 1.23)
Diabetes				1.13 (0.39, 3.25)
SBP				1.01 (1.00, 1.03)
Cholesterol				0.96 (0.71, 1.29)
WHR				50.77 (0.46, 5,620.33)
Smoking				
Former				0.91 (0.45, 1.84)
Sometimes				0.93 (0.21, 4.17)
Current				1.62 (0.66, 3.93)
Age				1.13*** (1.10, 1.17)
R^2_D		0.13	0.18	0.63
Log Likelihood		-399.69	-397.33	-350.28
Wald Test		10.91** (df = 2)	16.60** (df = 4)	81.47*** (df = 12)
LR Test		11.22** (df = 2)	15.94** (df = 4)	110.04*** (df = 12)
Logrank Test		11.46** (df = 2)	17.21** (df = 4)	98.83*** (df = 12)

Note. **p* < .05; ***p* < .01; ****p* < .001. SBP = Systolic blood pressure. WHR = waist hip ratio. LR = Likelihood ratio. Model 1: Combined effects of personality traits. Model 2: Model 1 + effects of mood disorder symptoms. Model 3: Model 2 + all risk markers. Pseudo R^2 is calculated according to Royston and Sauerbrei (2004). Baseline for smoking is n*ever*.

In the final model with all covariates, none of the psychological variables had an effect. For women (Table 3), neuroticism and depression initially had simple effects on stroke. In Model 1 neuroticism still had an effect, but this disappeared in Model 2. Here depression significantly increased the risk of stroke while anxiety decreased it. In the final model, extraversion was the only psychological variable that significantly impacted the risk of stroke, i.e. increasing the risk. When looking only at the men (Table 4), in terms of simple effects, extraversion significantly reduced the risk of stroke while depression significantly increased it. In Model 1, only extraversion had a significant, negative, impact on stroke. This effect carried over to Model 2, where depression also had a significant, but positive, impact on risk of stroke. In the final Model 3, none of the psychological variables had a significant impact on risk of stroke.

Discussion

In this study we measured extraversion and neuroticism, and symptoms of depression and anxiety during 2006-2008, with an average follow-up time of 10.48 years. While adjusting for all covariates, neuroticism and depression was associated with an increased risk of MI in the total sample. For men, but not for women, neuroticism retained its association with increased risk of MI. The impact of psychological variables on stroke were less evident. In the fully adjusted models, only extraversion was associated with a change in the risk of stroke, and for women only.

Given that depression has repeatedly been shown to increase the risk of CVD and CHD (Harshfield et al., 2020; Wu & Kling, 2016), it was unexpected that it only affected the risk of MI, and only in the total sample. The effects of anxiety on CVD are less certain, though some recent studies have found that anxiety also increases the risk of CVD (Batelaan et al., 2016; Pérez-Piñar et al., 2017). Our study does not support this, but rather supports the notion that anxiety does not impact CVD risk independently of depression, a finding consistent with other studies including both anxiety and depression as predictors (Karlsen et al., 2020).

The results are comparable to those of Jokela et al. (2014), as we found that extraversion was linked to increased risk of stroke, though only for women. Likewise, we also found that neuroticism was linked to CHD (in our case MI). One possible reason for the lack of observed effect of depression, is that personality is more stable than the more mutable affective conditions of depression and anxiety. Personality are a set of stable characteristic patterns of thought, cognition and behaviour (McCrae & Costa, 2010), while depression and anxiety are departures from normal functioning and the target of treatment with the goal of returning to the condition pre-existing the disorders. As neuroticism and extraversion both are predictors of depression (Kotov et al., 2010; Ormel et al., 2013; Watson et al., 2015), and share underlying biological basis (Markon et al., 2005), it is plausible that these account for the previous observed ef-

fect of depression in prior studies not including personality, supported by the finding of high stability in symptom level of anxiety and depression over long time-interval (Langvik & Hjemdal, 2015).The tendency for the previously significant effect of psychological variables disappearing after adding covariates to the model emphasise the importance of including relevant covariates and known risk factors when investigating the effect of psychological risk profiles.

Few studies have examined sex and gender differences in CVD risk, and updated guidelines on CVD prevention (Visseren et al., 2021) highlights the importance of investigating the role of psychological factors independent for men and women. We found that personality traits had unique effects for men and women: neuroticism was related to risk of MI for men, and extraversion was related to risk of stroke for women. This supports the notion of treating men and women as separate populations in the investigation of psychological risk profiles for CVD, as well as addressing the importance of separate analysis for different CVD outcome like MI and stroke.

Strengths and Limitations

We restricted the analyses of MI and stroke to those who died of MI or stroke. Differing effects may be found when examining CVD morbidity and mortality (Karlsen et al., 2021). Thus, these results cannot be extrapolated to MI/stroke morbidity. As the HADS excludes somatic symptoms of anxiety and depression, effects of somatic-type depression can be hidden.

Among the strengths of the study is the large size of the sample. While MI and stroke are common causes of death, the occurrence of these events are still relatively rare in a normal population, necessitating a large sample to detect effects. Although the measure of personality used in this study is validated, a more comprehensive measure of personality, preferably including other possible relevant traits, would be preferable. The focus on specific CVD outcomes separately for men and women, including both personality and symptoms of anxiety and depression represent a major strength of this study.

Conclusion

In this study we investigated the role of the personality traits neuroticism and extroversion along with anxiety and depression as gender-specific risk factors for stroke and MI, controlling for established risk factors of CVD. The results showed that extraversion was a significant predictor for stroke among women only, and that neuroticism was a significant predictor of MI among men, but not women. Anxiety and depression were not a significant predictor in the adjusted models, and it is suggested that dispositional factors play a prominent role in the understanding of sex- and gender-specific psychological risk profiles for stroke and MI.

Data sharing statement

The data used in this study is owned by separate public entities in Norway. The data is available upon request from the health registries of the Norwegian Institute of Public Health and the HUNT Study respectively. Note that a Norwegian researcher must be involved with the project to apply to HUNT. For more information, see here: https://www.ntnu.edu/hunt/data

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