Psychological Resources and Risk Factors in Coronary Heart Disease

Assessment, Impact and the
Influence of Mindfulness Training

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To Cecilia, Julian & Tilda

Pay attention now:
A heart that's all by itself is not a heart

~

Beyond living and dreaming
there is something more important:
Waking up

Antonio Machado
(1875-1939)

Moral proverbs and folk songs
Translated by Robert Bly
1983

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ABBREVIATIONS

ACS	Acute Coronary Syndrome
ACT	Acceptance and Commitment Therapy
AD	Anno Domini
AEs	Adverse Events
ANS	Autonomous Nervous System
Apo-B	Apolipoprotein-B
BC	Before Christ
BDI	Beck Depression Inventory
BDNF	Brain-Derived Neurotrophic Factor
BMI	Body Mass Index
CABG	Coronary Artery By-pass Graft surgery
CI	Confidence Interval*
CHD	Coronary Heart Disease
CNS	Central Nervous System
CRP	C-Reactive Protein
CVD	Cardio Vascular Disease
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electro Cardiogram
GAD-7	Generalized Anxiety Disorder-7
HAD	Hospital Anxiety and Depression
HPA	Hypothalamic Pituitary Adrenal
HRV	Heart Rate Variability
IL-6	Interleukine-6
IPT	Interpersonal Psychotherapy
LVEF	Left Ventricular Ejection Fraction
LSH	Life conditions, Stress and Health
MBIs	Mindfulness Based Interventions
MBCT	Mindfulness Based Cognitive Therapy
MBSR	Mindfulness Based Stress Reduction
MIMIRA	Mindfulness Intervention as Myocardial Infarction Rehabilitation Additive
MQ	Maastricht Questionnaire
PDT	Psychodynamic Therapy
PCA	Principal Component Analysis
PCI	Percutaneous Coronary Intervention
PHQ-9	Patient Health Questionnaire-9
RCT	Randomized Controlled Trial
RR	Relative Risk*
rTMS	repetitive Trans-cranial Magnetic Stimulation
SAD	Social Anxiety Disorder
SCID	Structured Clinical Interview
SES	Socioeconomic Status
SNRI	Selective serotonin and Noradrenalin Re-uptake Inhibitor
SOC	Sense of Coherence
SSRI	Selective Serotonin Re-uptake Inhibitor
5-HT	5-hydroxytryptamine

** Results from cited studies have, when possible, been reported as relative risk (RR) or hazard ratio (HR) estimates with 95 % confidence intervals (CI). For readers who lack statistical experience, it could be of value to know that the interpretation of these numbers is fairly easy: 1.0 represents no increased or decreased risk, 2.0 represents doubled, or 100% increased risk. Thus, a HR of 0.62, which was the decreased 8-year CHD risk for every 3.4-point improvement in Mastery reported in Study 2, represents a reduced risk of 38 %.*

LIST OF STUDIES

Study I

Inverted Items and Validity: A Psychobiological Evaluation of Two Measures of Psychological Resources and One Depression Scale

Oskar Lundgren, Peter Garvin, Lena Jonasson, Gerhard Andersson, and Margareta Kristenson
Health Psychology Open (SAGE), 2018: 5, 1-9.

Study II

Psychological resources are associated with reduced incidence of coronary heart disease. An 8-year follow-up of a community-based Swedish sample

Oskar Lundgren, Peter Garvin, Lena Jonasson, Gerhard Andersson, and Margareta Kristenson
International Journal of Behavioural Medicine, 2015: 22: 77–84.

Study III

Mindfulness Based Stress Reduction for Coronary Artery Disease Patients: Potential Improvements in Mastery and Depressive Symptoms

Oskar Lundgren, Peter Garvin, Lennart Nilsson, Viktor Tornerefelt, Gerhard Andersson, Margareta Kristenson, and Lena Jonasson
Submitted manuscript

Study IV

A journey through chaos and calmness: Experiences of mindfulness training in patients with depressive symptoms after a recent coronary event - a qualitative diary content analysis

Oskar Lundgren, Peter Garvin, Margareta Kristenson, Lena Jonasson, and Ingela Thylén
Manuscript under review (BMC Psychology)

ABSTRACT

There is strong evidence for the observation that psychological risk factors, such as depressive symptoms, hopelessness, and anxiety are associated with higher risk of developing coronary heart disease (CHD), and also contribute to a worse prognosis among CHD patients. Much less is known about psychological resources, such as Mastery, and their role in cardiovascular medicine. Although the current state of science about the importance of psychological factors has advanced during the last decades, the mental health status of patients is often neglected in clinical practice. The reason behind this gap is multifaceted, including unawareness of the current state of science among professionals and a lack of clear guideline, which in turn, results from a lack of evidence-based ways to address the issues. Furthermore, the measurement of psychological resources is complex and a debated topic in psychology. The aim of this thesis was to investigate: 1) If the use of inverted items in three questionnaires that measure psychological resources and risk factors represent a validity risk in the context of CHD. 2) If psychological resources and risk factors are independently associated with incidence in CHD. 3) If an eight-week course in Mindfulness-Based Stress Reduction (MBSR) is a feasible psychological intervention, as an addition to cardiac rehabilitation. 4) How CHD patients experience the practices of mindfulness and yoga in MBSR.

In *Study I* and *II*, data from 1007 participants randomly selected from a Swedish community sample, aged 45-69 at baseline (50 % women), were analysed. To study the validity of the self-report instruments Mastery, Self-esteem and Centre for Epidemiological Studies Depression scale (CES-D), subscales with only positive and negative items were created. The new subscales were evaluated against three criterion measures; cross-sectional against each other and the circulatory marker of inflammation interleukine-6 (IL-6) (*concurrent construct validity*); prospectively against 8-year incidence in CHD (*predictive validity*), and in addition, a factor analysis was used to investigate *construct dimensionality*. The instruments seemed to be valid measures of psychological resources and risk factors in the context of CHD risk. The new subscales showed the same associations as the original scales, except for the positive items in CES-D. However, this did not have a major influence on the full scale. In *Study II* a prospective analysis of the impact of psychological factors on 8-year incidence in CHD was performed. The psychological resources Mastery and Self-esteem were negatively associated with CHD, also after adjustment for nine traditional cardiovascular risk factors in Cox proportional hazard models. The protective effect of the two resources, and the increased risk of Hopelessness, remained after adjustment for depressive symptoms. In *Study III* and *IV*, a group of CHD patients with depressive symptoms (n=79) was invited to participate in MBSR as a complement to cardiac rehabilitation. Twenty-four patients started MBSR and 16 completed it. The results were compared with a reference group (n=108) of patients from the same clinic, which showed stability in psychological variables over 12 months. MBSR was appreciated by the patients and improvements in psychological risk factors (e.g., depressive symptoms), and an increase in Mastery were observed. *Study IV* made use of a qualitative content analysis of diary entries written by patients immediately after practice sessions throughout MBSR. Participants described difficulties, both physical and psychological, during the whole course, but as the weeks passed they more frequently described an enhanced ability to concentrate, relax and deal with distractions. From the combined findings in *Study III* and *IV*, we conclude that MBSR could be a promising complement to cardiac rehabilitation for a selection of patients.

The overall picture, emerging from this thesis, strengthens the argument that psychological factors should be recognized and addressed in clinical practice. It also encourages further studies of how psychological resources could be built, which could inform the development of effective prevention and treatment strategies for CHD patients with psychological distress and also contribute to improved public health interventions.

SVENSK SAMMANFATTNING

Det är väl belagt att psykologiska riskfaktorer, såsom depressiva besvär, hopplöshet och ångest, är kopplade till risken att utveckla kranskärslssjukdom. De bidrar även till en sämre sjukdomsprognos. Mindre är känt om vilken roll psykologiska resurser, t.ex. copingförmåga, spelar för risken att drabbas av kranskärslssjukdom. Även om kunskaperna om betydelsen av psykologiska faktorer har ökat avsevärt de senaste årtiondena så har patienters psykiska hälsa ofta negligerats i den kliniska vardagen. Anledningarna till detta är mångfacetterade och inkluderar en bristande kännedom om kunskapsläget hos professionerna samt en brist på tydliga riktlinjer, vilket kan bero på att effektiva metoder att göra något åt saken saknas. Därutöver är det omdebatterat hur man bäst mäter psykologiska variabler. Syftet med denna avhandling var att studera: 1) Om användandet av omvända frågor i tre instrument som mäter psykologiska resurser och riskfaktorer utgör en risk för instrumentens validitet i en hjärtkärlkontext. 2) Om psykologiska resurser och riskfaktorer är oberoende associerade med insjuknande i kranskärslssjukdom. 3) Om en åttaveckorskurs i mindfulness-baserad stresshantering (MBSR) är en genomförbar intervention, som komplement till hjärtrehabilitering. 4) Hur patienter med kranskärslssjukdom upplever övningarna i MBSR.

I *Studie I* och *II* analyserades data från 1007 deltagare, 45-69 år gamla vid studiestart (50 % kvinnor), som var slumpvis utvalda från befolkningen i Östergötland. För att studera validiteten hos frågeformulären *Upplevd copingförmåga* (Mastery), *Självkänsla* (Self-esteem) och *Depressiva besvär* (Centre for Epidemiological Studies Depression, CES-D), delades de upp i skolor med enbart positiva och negativa frågor. De nya delskalorna utvärderades gentemot tre validitetskriterier. Först i tvärsnittsanalyser gentemot de andra psykologiska variablerna och en cirkulerande markör för inflammation; interleukin-6 (IL-6) (*samstämmig validitet*). Därefter prospektivt gentemot 8-års risk för insjuknande i kranskärslssjukdom (*prediktiv validitet*). Därtill gjordes en faktoranalys som undersökte *dimensioner* i instrumenten. De positiva och negativa delskalorna gav samma utfall som originalen, med undantag för de positiva frågorna i CES-D, vilka dock inte verkade påverka originalskalans validitet. Sammantaget verkade mätinstrumenten vara tillförlitliga i en hjärtkärlkontext. I *Studie II* gjordes en prospektiv analys med Cox regressionsmodeller av psykologiska faktorer påverkan på 8-årsrisken att insjukna i kranskärslssjukdom. Resurserna *Upplevd copingförmåga* och *Självkänsla* hade en skyddande effekt, medan *Hopplöshet* var förenad med ökad risk. Associationerna ändrades inte av kontroll för nio kardiovaskulära riskfaktorer. Skyddseffekten för resurserna, och den ökade risken för *Hopplöshet*, kvarstod även efter kontroll för depressivitet. I *Studie III* och *Studie IV* inbjöds en grupp nyligen insjuknade kranskärslspatienter med depressiva symptom (n=79) till en MBSR-kurs som komplement till hjärtrehabilitering. Tjugofyra deltagare påbörjade MBSR och 16 avslutade. Resultaten jämfördes med data från en referensgrupp (n=108) av patienter från samma hjärtmottagning, i vilken psykologiska variabler vid en 12-månaders uppföljning var oförändrade. Deltagarna uppskattade MBSR-kursen och en minskning av riskfaktorer (bl.a. depressivitet) och en förbättring av *Upplevd copingförmåga* observerades. I *Studie IV* analyserades dagboksanteckningar, som 12 av de 16 deltagarna skrev i anslutning till övningarna, med kvalitativ innehållsanalys. Deltagarna beskrev svårigheter, såväl fysiska som psykiska, under hela kursen, men alltmedan veckorna gick beskrev de oftare en stärkt förmåga att koncentrera sig, slappna av och hantera distraktioner. Sammantaget talar resultaten för att MBSR skulle kunna vara ett lovande komplement till dagens hjärtrehabilitering för ett urval av patienter.

Den samlade bilden från denna avhandling stärker argumentationen att psykologiska faktorer bör uppmärksammas i det kliniska arbetet med kranskärslspatienter. Fynden uppmuntrar även till fortsatta studier av hur psykologiska resurser kan stärkas, vilket kan leda till utvecklingen av effektivare metoder att förebygga och behandla psykisk ohälsa hos kranskärslspatienter och i befolkningen.

PREFACE

The completion of a PhD-thesis is a journey of apprenticeship in the craft of doing research, and I guess this journey is unique for every single student who embarks on this path. My journey began almost a decade ago, when my supervisor on a scientific project in medical school asked me if I would like to write articles together with her, instead of writing news articles about sports- and cultural events (which was how I was earning my living during the second half of medical school). This journey through the academic terrain has been more challenging and exciting than I could have imagined. It has been simultaneously rewarding and exhausting to knit it together with the other paths I have trodden during this period of my life; including half a decade of a paediatric internship, getting married, building a house and becoming a father of two amazing kids, as well as losing two four-legged members of my pack.

These years have offered me a marvellous and crazy mix of studying, commuting, taking care of patients, writing, teaching, publishing (and getting rejection e-mails), sitting in meditation, running in the Alps and also doing nothing at all. Periods of insane amounts of work have been intermingled with invigorating visits to retreat centres and meditation teachers in both Sweden and the United States. These experiences have brought me a degree of freedom in the midst of all that might have been lifesaving. But they have also allowed me to taste the bittersweet irony of being a stress-researcher with too many pressures and a mindfulness instructor with too many strings on his lute. Some days one can laugh about this predicament, other days one is closer to tears.

One could easily see some resemblances between my journey and the interdisciplinary field of *behavioural cardiology*. The many parallels and loose strings of research, which with time have been woven together into a somewhat coherent piece of knowledge, have come from laborious efforts from a large number of researchers and many thousands of patients during centuries of scientific exploration. The work behind the four studies in this thesis comes from collaborative efforts of a research group with diverse skills and personalities, and any contributions to science that are to be found in the letters and numbers written in the four manuscripts, are the fruit of a dynamic group process. We have not only stood on the shoulders of scientific giants, but also on each other's experience and creativity.

My greatest hope with this thesis is that the small amount of additional clarity, that our studies may have contributed with, will result in the ease of suffering among future human beings who end up as patients in the cardiac unit at hospitals around the world.

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Linköping
June 2018

AIMS

The overall aim of this thesis was to study the assessment and impact of psychological resources and risk factors in coronary heart disease (CHD). Furthermore, it also explores a novel way to translate the growing knowledge of the importance of psychological variables in CHD into the clinical reality of cardiac rehabilitation. These two general aims have been translated into four research questions:

- I.* Does the use of inverted items in the self-report instruments Mastery, Self-esteem, and CES-D (depressive symptoms), represent a validity risk when the questionnaires are used in the context of CHD risk?
- II.* Are psychological resources and risk factors independently associated with the eight-year incidence of CHD?
- III.* Is Mindfulness-Based Stress Reduction a feasible and acceptable intervention for CHD patients with depressive symptoms after a recent coronary event? And furthermore, does the intervention have any long-term effects on Mastery and depressive symptoms?
- IV.* How do patients with CHD and depressive symptoms experience the practices of mindfulness meditation and yoga during Mindfulness-Based Stress Reduction, and how do these experiences relate to potential benefits from and barriers for the practice?

BACKGROUND

PART I

CORONARY HEART DISEASE

1. A Brief History of Coronary Heart Disease

When George August of Hanover, King of Great Britain and Ireland, and Duke of Brunswick-Lüneburg, woke up at six a clock 25 October 1760, he probably knew that his most glorious days were behind him. He was 77 years old, had withdrawn his attention from political life, and his health was slowly deteriorating. According to historical records, the aged king is said to have gathered forecasts of the weather and made some vague plans for a walk in the garden of Kensington Palace. He then retreated to the royal bathroom. After a while, his attendant heard a noise, and when he entered the bathroom, he found George lying on the floor, motionless and with a deep wound in his head. Within minutes, George II took his last breath [1]. George II's body was examined by his physician Franch Nicholls (1699-1778) and he found the cause of death to be a rupture of the right ventricle in George's heart, and also a large aortic dissection. When the historian Joshua Leibowitz summarized the history of coronary heart disease (CHD) in 1970, he argued that this autopsy could have been the first accurate description of a myocardial infarction, but Dr. Nicholls did not mention the coronary arteries in his report [2].

There is little doubt that CHD has accompanied the human species during most of its somewhat short appearance on earth. But since the circulatory system is exclusively made up of soft tissues, they are usually not possible to study by archaeologists who dig up and analyse the remnants of prehistoric humans [3]. However, in instances where the deceased has been mummified it is possible to examine the heart and its vessels, and indeed, some archaeologists have found sclerotic changes in the coronary arteries of Egyptian mummies [3].

Even though the correct identification of the occluded coronary artery as the cause of the syndrome of angina pectoris (chest pain) was understood surprisingly late, earlier generations of physicians had grasped at least some pieces of the puzzle. References to the clinical signs of precordial pain have been found in papyruses from ancient Egypt (~3000 B.C.) as well as in the Bible (~400 B.C. – 100 A.D.) and the Talmud (~500 A.D.). Hippocrates (~400 B.C.) mentions obstruction of blood flow, as a potential disease mechanism and Claudius Galenus (129-199 A.D.) is famous for his clear description of the coronary vessels and their function of delivering nutrients. Leonardo da Vinci (1452-1519 A.D.) created detailed drawings of the heart and the coronary arteries but made no references to the pathological processes of calcification and occlusions. William Harvey (1578-1657), had revolutionized the study of physiology with his clear description of how blood circulates in the body, but the mechanism behind CHD were not discovered until almost two hundred years later [4].

A great leap in the understanding of myocardial infarctions was made almost simultaneously with the death of King George II. The famous internist William Heberden (1710-1801) published his article *Some accounts of a disorder of the breast* in 1768, and it contained a clear description of myocardial infarctions, but without references to the coronary arteries. In 1799 the picture finally cleared when Edward Jenner and C. H. Parry, both published texts that elaborated the central role of obstructed coronary artery blood flow [4].

2. The Global Burden of Coronary Heart Disease

Prevalence and incidence in CHD are often discussed in the broader context of *cardiovascular diseases* or CVDs, since this group of disorders have, to a large extent, the same risk factors and pathophysiological processes, and there are significant overlap and interactions in their respective consequences. CVD also includes *cerebrovascular disease*, which is diseases of the blood vessels supplying the brain and *peripheral artery disease*, which involves blood vessels supplying the arms and legs [5].

According to the World Health Organization (WHO), CVDs are the leading cause of death globally. In 2015, an estimated 17.9 million people died from CVDs, which represents 1/3 of all human deaths on the planet that year. Among these, 7.4 million died from CHD and 6.7 million died from cerebrovascular strokes. More than 75 % of these CVD deaths took place in low- to middle-income countries. In 2015, there were an estimated 423 million cases of CVDs [5].

There have been notable trends in the epidemiology of CHD during the 20th century. During the first half there was a sharp rise in incidence that peaked in the mid-1960s [6]. Since the 1970s, however, the developed parts of the world have seen a steep decline, and during the last 45 years, deaths from CHD have declined 50 % [7]. This positive trend has unfortunately been unevenly distributed between low- middle- and high-income countries, and not surprisingly the decline has been smaller, absent or reversed in low-income countries [8]. The variability in prevalence rate is high and the age-standardized country level of prevalence in 2015 varied between < 4000/100000 persons, to > 11000/100000 persons. Analyses of the latest estimates show that the rapid decline in countries with the highest level of development has plateaued and is no longer continuing. According to the authors of this recent analysis, these results demonstrate the importance of increased investment in prevention and treatment of CHD in all parts of the world [8]. This argument highlights the need for alternative ways to work with both prevention and treatment and evidence-based psychosocial interventions represent one route.

The burden of CHD is also unevenly distributed among different groups within both high- and low-income countries. More than three decades of research have consistently shown a predictive association between socioeconomic status (SES) and CHD [9]. SES is usually estimated from either level of education, occupational status, or income. The relative importance of SES compared to a large number of other risk factors, was recently investigated in a meta-analysis of 1.7 million participants. As expected, those with the lowest SES had greater mortality rate than those with the highest SES (HR 1.42 CI 1.38-1.45). The corresponding HRs for smoking, obesity and physical inactivity was 2.17, 1.04 and 1.60 respectively [10]. Sweden is one of the less afflicted countries in terms of incidence and death in CHD. In 2016, 25700 persons were diagnosed with a myocardial infarction. Among these, roughly 3600 died from their coronary event. This incidence translates into 352 new cases per 100000 inhabitants and year [11]. However, also in Sweden SES is related to the risk of CHD and the relative risk for those with low SES are doubled compared to those with high SES [11]. Many patients survive their myocardial infarction or stroke, and it has been estimated that roughly 1.8 million people in Sweden are living with a CVD, which correspond to almost 20 % of the population [12].

From all these numbers we can conclude that CHD affects a large number of people around the globe and that we have made enormous progress in the treatment of the disease. However, CHD and related vascular diseases remain the leading cause of death and represents an enormous source of suffering that comes with enormous personal and societal costs.

3. The Pathophysiology of Coronary Heart Disease

The first scholar to use the term *atherosclerosis* was Jean Frédéric Lobstein (1777-1835), but it would take almost another century until it became clear that the process leading to myocardial infarction contained both the “ossification” of the coronary artery and a thrombotic occlusion [4].

We now know that *atherosclerosis* is a disease process which starts early in life, sometimes even during the later stage of childhood, with the formation of so called *fatty streaks*, that appears in areas of the arteries where the wall are subjected to stress from turbulence in the blood flow. We also know that the immune system, with their different branches (innate and adaptive) and subsets of white blood cells (WBCs) (e.g., neutrophils, leukocytes, and monocytes), are critical players during all phases of the disease process [13].

There seems to be a wide range of factors that interact with genetic predispositions in certain individuals to initiate the first steps of the *atherogenesis*, and these include a high-fat diet (mainly saturated fatty acids), smoking, hypertension, hyperglycemia, insulin resistance and obesity [13]. How these factors exert their adverse effect is not entirely clear. Increased and dysregulated inflammation seems to be the crucial common pathway that propels the pathophysiological development. Recent studies of drugs that directly inhibit critical molecules in the inflammatory cascade, such as a blockade of the pro-inflammatory cytokine IL-1 β with an antibody called *kanakinumab*, have shown substantial primary preventive effects [14].

Usually, the cells that line the inside of our arteries (endothelial cells), do not allow WBCs to adhere to their surface and migrate into the inner layers of the artery wall. But when some of the above mentioned triggering factors stress the endothelium to the point of dysfunction, it begins to express adhesion molecules on their surface. One of the most potent inducers of adhesion molecules is the presence of oxidized lipids in the intima of the artery. These lipids come from a particular kind of cholesterol molecule called Low-density lipoprotein (LDL), and the ones which contain the apo-lipoprotein type B (Apo-B), are most likely to enter into the arterial wall and cause trouble when they become oxidized and thus more biologically active.

The *lipid core* is a central feature of what scientists call *pre-atheroma*. It represents a kind of middle-phase between the somewhat common and innocent so-called *fatty streaks*, and the final and more aggressive and dangerous *atherosclerotic plaque*. Over time, the pre-atheroma develop into a more mature and complex *atheroma*. This process is characterized by smooth muscle cell proliferation, further lipid accumulation and the development of a *fibrous cap* (constituting of extracellular matrix made up of collagen molecules mostly made by the smooth muscle cells). The immune system is a central regulatory factor that either accelerates or decelerates this development [15].

With a risk of simplifying complex processes, the further development of the atheroma could take one of two different developmental roads. The first path leads to the formation of a stable lesion that grows with a thick fibrous cap and leads to slowly developing stenosis of the particular coronary artery (in the case of CAD), while the second path leads to accelerated development of the lipid core and are characterized by a thin cap and thus, prone to rupture [16]. These two variants of CAD also give rise to different clinical pictures.

4. The Clinical Presentation of Coronary Heart Disease

A simple model of the complex process of how an atherosclerotic plaque proceeds to cause a *myocardial infarction* can be outlined in the following distinct steps [17]:

- + The atherosclerotic plaque grows larger and eventually begins to occlude the arterial lumen, obstructing the blood flow, which may or may not cause symptoms of chest pain (*angina pectoris*) when the heart muscle gets less oxygen than needed.
- + The plaque may erode or rupture. This leads to activation of thrombocytes and the formation of a blood clot (a *thrombus*).
- + If the artery becomes blocked by the *thrombus*, the part of the heart muscle that the artery was supposed to support with oxygen and serve with the removal of metabolic waste, gets deprived of oxygen (*ischemia*) and overflows with metabolic waste.
- + When a part of the heart muscle (the *myocardium*) becomes stripped of its oxygen supply for an extended stretch of time, the muscle cells will suffer damage, as its cells will start to die after seconds to minutes of oxygen-starvation.
- + Later on, dying and dead heart muscle cells can impede the heart's pumping function, and depending on the extent of the damage, this might lead to inadequate pumping ability, either in short- or the longer time frame.
- + The negative impact on the electric circuits, which usually orchestrates the synchronized movements of the muscle cells, can become so severed that the heart starts to "shiver" instead of pumping (called a *ventricle fibrillation*). This can result in sudden death, mere seconds or minutes after the thrombus occluded the artery.

Cardiologists have long been intrigued by the fact that myocardial infarctions often come without any warning signs such as earlier *angina pectoris* (chest pain). Indeed, studies have shown that it is seldom the slow-growing, calcified and stable atherosclerotic plaques that ruptures and cause an MI, but rather a different kind of plaques [17]. These plaques, sometimes called *vulnerable* (because they are vulnerable to rupture), are often located at multiple sites in the coronary arteries and often do not occlude the lumen before they burst.

Vulnerable plaques have a thinner fibrous cap over their lipid core, which often is more massive and bursting with inflammatory cells. Furthermore, they have fewer smooth muscle cells, which are the primary producers of collagen, a protein responsible for the flexible strength of the fibrous cap. Why some plaques develop into the vulnerable subtype is not entirely clear, but dysregulated inflammatory activity inside these plaques is the main hypothesis for the moment [14].

5. The Diagnosis and Treatment of Coronary Heart Disease

During the 19th-century, continuous advancement in the understanding of CAD shifted the focus of research activity from the coronary arteries to the myocardium and the damages produced during and after an infarction. It would also take surprisingly long time until the new knowledge was changing the practice of physicians [4].

A significant shift in this regard came with the invention of the electrocardiogram (ECG apparatus), by Willhelm Einthoven 1903, which rendered him the Nobel Prize in medicine 1924. During the first two decades of its use the technology was clumsy, expensive and mostly used for scientific endeavours. However, at the time Einthoven went to Stockholm for the Nobel ceremony, the device had shrunk into 1/30 of its original weight and soon became a much valued and available diagnostic tool around the world [4].

Almost simultaneously with the development of the ECG-machine, laboratory tests that could aid clinicians in the diagnostic process were developed. The first useful observation was that the fraction of WBCs was increased very soon after a myocardial infarction. Shortly after, the sedimentation rate (SR) was described as an accurate method to assess improvement or recovery [4].

During the second half of the 19th-century, discoveries of enzymes (e.g., *transaminases*) as biomarkers of myocardial damages became widely used, although these test had shortcomings in their specificity. The cardiac-specific biomarkers *Troponin-I* and *Troponin T* have excellent sensitivity and elevations are detectable in the circulation within 2-3 hours and peak within 24-28 h. In the acute situation, cardiologists use risk stratification systems to select those in need of the most aggressive forms of treatment [18].

The spectrum of more or less acute clinical presentations of CHD is usually covered under the umbrella term *acute coronary syndrome* (ACS), which in addition to the classical *myocardial infarction* (MI), also include *unstable angina pectoris* (which sometimes require invasive intervention and subsequent rehabilitation). Two hundred years ago, almost 2/3 of patients hospitalized for MI died at the hospital. Today, thanks to early pharmacological, invasive interventions, and multidisciplinary intensive care units, that number is reduced to about 7 % [19]. However, almost half of those who die from a MI, do so outside of the hospital. Furthermore, sudden death in CHD is more common among younger subjects, which makes prevention important [20].

Fibrinolytic agents are drugs that increase the conversion of plasminogen to plasmin, which lyses fibrin and a thrombotic clot can dissolve. They have been available since 1976, and were the treatment of choice before the advent of acute invasive therapies. Fibrinolytic treatment has been estimated to reduce mortality by almost 30 %, but is associated with adverse effects, such as the risk of bleeding, and when Percutaneous Coronary Intervention (PCI) became widely available it has replaced fibrinolysis in most situations. In 2003, Keely et al. published a meta-analysis of 23 trials with primary PCI vs. fibrinolysis, and found the former superior in both the prevention of short-term major adverse cardiac events and with long-term preventive effects [21].

Percutaneous Coronary Intervention, first performed on a patient in 1977, is a procedure where the operator, generally a cardiologist, inserts a thin catheter into an artery of the lower arm, or the upper leg, of a patient that is usually awake but briefly sedated. The catheter follows a large artery to the aorta, and when it reaches the place where the aorta is attached to the left ventricle, the operator can enter into the coronary arteries. There a thrombus could be captured into a small

metal fishing net, or forked with a small hook and withdrawn from the coronary artery. The purpose of this procedure is to restore blood flow to the oxygen and nutrient-starved myocardium, and oftentimes the operator inserts a metal stent to secure an open vascular lumen [22].

The first *Coronary Artery Bypass Graft* (CABG) surgery procedure was made in 1969, and although PCI has replaced this complicated open-chest operation, it still has a place in patients who do not respond to PCI or who have complications such as ruptures of their myocardial septae. Furthermore, CABG still has a place in the secondary prevention, and symptoms reduction for patients with unstable- and stable angina pectoris, heart failure, multi-vessel disease or have difficulties tolerate anti-platelet therapy. CABG is a procedure where one or more of the patients coronary arteries are replaced with a graft; either autologous (a vessel harvested from another location in the patients own body) or a blood vessel from a donor or animal [22].

The treatment of ACSs is more or less always complemented with *pharmacological agents*, and the goal is to limit the damages from ischemia (e.g., myocardial remodelling) and to prevent future acute coronary events (e.g., by addressing known risk factor). A detailed review of these pharmacological agents is beyond the scope of this introduction, but the most commonly used should be mentioned here. These drugs aim to lower the blood pressure and prevent unwanted myocardial remodelling (Beta-blockers, Angiotensin converting enzyme inhibitors and Aldosterone antagonists) and reduce blood lipids (Statins). Patients also get a loading dose of *aspirin*, followed by a continuous low dose, which has substantial antiplatelet effects, and a newer antiplatelet drug called *ticagrelor*, that inhibit platelet aggregation. Sometimes two antiplatelet drugs are combined with another type of anticoagulant medication (called triple antithrombotic therapy). Some patients with increased risk of fatal arrhythmias, gets an implantable cardioverter-defibrillator (ICD), which can further prevent sudden cardiac death in vulnerable patients [18].

The four studies included in this thesis do not focus on research questions related to invasive or pharmacological treatment. However, all patients recruited and included in *Study III* and *IV* had underwent an invasive procedure and received the standard drugs for secondary prevention. An awareness of these current practices is also crucial for the research that this thesis is focused on for other reasons as well. Drug treatment could have psychological side effects that could act as confounding factors when the relationship between psychological variables and disease outcome is investigated. Furthermore, compliance with the recommended drug regimen might represent an indirect mechanism that mediates the relationship between psychological distress or well-being and CHD. These two potential sources of bias have not been measured in any of the included studies, but their existence should be on the radar screen when interpreting the results.

Even though we have a fairly precise knowledge of the gradual development of atherosclerosis, and of risk factors that catalyse this pathophysiological downward spiral, the progress in the area of prevention has been less impressive. Much is known about how CHD could be prevented among apparently healthy people, and how the prognosis could be improved among CHD patients. But there is a significant gap between what we know in theory and our ability to help people and patients to manage their risk factors. This gap is telling us that much more research of preventive cardiology is needed, and a further exploration of psychological resources and risk factors could represent an important advancement forward.

6. The Determinants of Coronary Heart Disease

During the 1950s and 60s, cardiologists and epidemiologists began to better understand what causes CHD. The establishment of the famous Framingham Heart study in 1948 was a pivotal piece to the puzzle. In the 1960s it had become clear that both hypertension and hyperlipidaemia were strong risk factors and soon, thanks to new pharmacological inventions, also preventable ones [19]. Since the first risk factors were discovered, science has produced a rather long list of both preventable and not so much preventable (e.g., genetic) risk factors that both increase the risk of incidence [23] and that contribute to subsequent disease events and mortality in patients with established CHD [24]. The discovery in the 1980s that atherosclerosis is an inflammatory disease have further informed our use of risk predictors. With the introduction of biomarkers of disease risk such as *C-reactive protein* (CRP) and the pro-inflammatory cytokine *Interleukine-6* (IL-6) (the inducer of CRP synthesis) [25,26], as well as ratios of white blood cells called neutrophils and lymphocytes (NLR), clinicians had new tools to evaluate risk of future CHD [27].

The international multi-centre case-control study INTERHEART, investigated 15152 MI patients and 14820 controls. It showed that, in addition the traditional risk factors of hyperlipidaemia (here measured as ApoB/ApoA-ratio), hypertension and diabetes mellitus, the following preventable risk factors were also important; smoking, abdominal obesity, intake of fruit and vegetables, physical activity, alcohol intake, and psychosocial factors (a composite measure of depression, control, perceived stress and life events). Together these nine risk factors explained 90 % of the variance between groups that have or have not the measured risk factors [23].

Iestra et al. summarized the evidence for secondary preventive effects of interventions that address risk factors among patients with established CHD [24]. The authors pooled the results from 3 meta-analyses, 10 RCTs and 9 cohort studies and calculated estimated risk reductions in mortality. The authors estimated the following risk reductions: *smoking cessation*: ~35 %; *habitual physical activity*: ~25 %; *moderate alcohol consumption*: ~20 %; *reduction of saturated fat intake*, with subsequently *lowered serum cholesterol*: ~12-25 % [24].

The importance of health behaviours for sustained health has become increasingly recognized in the medical sciences. Recently, Li et al. reported combined data from the Nurse's Health Study and the Health Professionals Follow-up Study, and estimated life expectancy from the scores of a healthy lifestyle index comprising of never smoked, having normal BMI, exercise > 30 min/day, a moderate amount of alcohol and a healthy diet. The increased life expectancy for those who had all the good habits, compared to those who had none of the good habits, was 14 years for women and 12.2 years for men. The authors conclude that prevention should be a top priority for national health policy and preventive care should be an indispensable part of the healthcare system [28].

Psychological resources and risk factors are sometimes included in the list of preventable risk factors (e.g., in the INTERHEART study), and sometimes not. In a recent review article, Alan Rozanski described the separation of health behaviours (e.g., diet and physical activity) and psychological risk factors (e.g., depressive symptoms), as an *artificial divide*, and argued against a separation where physical activity and diet are called conventional risk factors [29].

7. Cardiac Rehabilitation

A widespread and evidence-based way to help patients with lifestyle changes, and adherence to pharmacological treatments, is *cardiac rehabilitation*. It is offered to most newly diagnosed CHD patients, at least in developed countries. The rehabilitation program is usually built around regular visits with a cardiac nurse, and the follow-up of medication and traditional risk factors are often complemented with individual prescriptions of physical activity and advice about lifestyle [30].

A recent Cochrane review and meta-analysis found 63 studies with 14486 participants, with a mean follow up of 12 months. The meta-analysis showed that cardiac rehabilitation, compared to only usual care, led to a reduction in cardiovascular mortality (RR 0.74, CI 0.64-0.86), and a reduction of future hospital admissions (RR 0.82 CI 0.70-0.96). However, the analysis revealed no significant effect on total mortality, subsequent MI or the need for revascularization procedures [30]. Another recent Cochrane review and meta-analysis limited the analysis to patients with stable angina pectoris and found 7 studies with 581 participants. The authors concludes that the evidence for effects was of very low quality, making it uncertain if there are any reliable effects, and they argued that there is a need for more and well-designed trials [31].

The cardiac clinic in Linköping, from which the participants of *Study III* and *IV* were recruited, offer their patients a year-long participation in cardiac rehabilitation which includes; 1) Work capacity test with physiotherapist: 2) Exercise in group. 3) Heart school (three group meetings with education in CHD diagnoses, diet, exercise, drugs and psychological reactions). 4) Follow-up visits with cardiac nurse within a month and a cardiologist at 2-4 months, and again to the nurse at 12 months. 5) Smoking cessation counselling. 6) Consulting with dietician or social worker. 7) Stress School (12 months of group discussions). The stated goal of the cardiac rehabilitation is to regain a good quality of life and an active life, and the risk of a secondary cardiac event should be lowered through lifestyle changes and long-time pharmacological therapy [32].

The main problem with cardiac rehabilitation is that only a small percentage of patients change their health behaviour after taking part of rehabilitation. According to a recent international survey by Koteseva et al. in 2016, the majority of patients in cardiac rehabilitation do not achieve the goals of the rehabilitation program, and many continue to smoke, eat unhealthy food and live sedentary lives, with resulting overweight and metabolic disturbances [33].

This unsatisfactory gap between what we know would help our patients and what is accomplished during cardiac rehabilitation is indirectly connected to the aims of this thesis since changing health behaviour is a multifaceted psychological process that is related to complex processes of self-regulation and motivation. Furthermore, psychological symptoms such as depression and anxiety, as well as psychological resources such as self-esteem and mastery might influence the process of behaviour change. This particular question is not the focus of any of the four studies in this thesis, but the findings may have implications for successful health behaviour change, and future research is suggested on the basis of this possible connection. Furthermore, *Study III* and *IV* investigate the feasibility of complementing cardiac rehabilitation with mindfulness and yoga practices, and the possibility that a mindfulness-based psychological intervention could become a unifying bridge between methods to address psychological factors and health behaviours is discussed.

A NOTE ON TIME FRAMES IN THE STUDIES

When researchers study psychological risk factors in relationship to CHD, they have to dismantle if the psychological trait or state was present during all the years it took to develop severe atherosclerosis, if it was a newly occurring phenomenon just before the first ACS, possibly influencing the vulnerability of the atherosclerotic plaque, or if symptoms were debuting in the aftermath of the acute event, representing a psychological sequelae.

With the exception of depressive symptoms, studies of *psychological sequelae* from the experience of ACSs, like onset of anxiety disorders and post-traumatic stress syndromes, are very few and patients suffering from these consequences are often not detected and treated [34]. The narrow time frame of days or even hours has been more extensively studied, and a broad range of factors – including psychological – have been shown to be able to trigger a coronary event [35]. This is an exciting area of investigation and earlier studies have shown that anger, anxiety attacks, grief, work-stress, natural catastrophes, and even emotionally charged sporting events could trigger an acute coronary event [36].

A fascinating example is the 1996 European championship in soccer, which was won by France, who beat Holland after penalties. On this day the relative risk of MI for Dutch men was 1.5 (CI 1.1-2.1), but not for Dutch women or French people of both sexes. In addition to these psychological triggers, it is known that heavy physical exertion, lack of sleep, sexual activity, infections, heavy meals, drugs, and exposure to cold in the winter season, can also trigger MIs. The studies included in this thesis did not study psychological factors as triggers of, or sequelae from, acute coronary event, and these topics are therefore not reviewed in further depth [36].

The methodological challenges of separating more stable traits from fleeting states, and disentangle slowly acting mechanisms from triggering factors, are great and require humble considerations of study design and interpretation of results. In *Study I* and *II* in this thesis, the aims were to investigate the longitudinal influence of rather stable traits, such a sense of Mastery and Self-esteem. However, since the outcome was first time coronary event there could have been some kind of environmental triggers involved. *Study III* and *IV* evaluated psychological variables in the time frame of month to years after the coronary event, and also after participation in a psychosocial intervention. In these studies, the possibility that the psychological variables measured were influenced by the recent, possibly traumatic, experience of becoming seriously ill needed to be handled. These considerations were taken into account in decisions about when and how to measure psychological factors among the patients.

PART II

PSYCHOLOGICAL FACTORS & CORONARY HEART DISEASE

8. Psychology and Psychosomatic medicine

Before the spark of scientific revolution was lit during the age of enlightenment, around mid 17th century, religious authorities were usually providing answers to questions about where to find, and how to explain the psychological aspects of human beings (e.g., thoughts and emotions). The common understanding during this period was that our mind and its content were expressions of our possession of an immortal soul. Although a few philosophers and atheists contested this view, they usually argued for alternative relationships between a human spirit and its surrounding universe, and the idea that our minds and emotions could be dependent on a physical organ floating inside our skull would have been deemed absurd [37].

Instead, it was the heart that was usually associated with both intelligence and emotions. This tradition goes back to the old Egyptians that kept the heart intact when preparing their dead for the afterlife. The philosophers of ancient Greece shared this idea, and many of them believed that the soul housed in the heart during its time in the body. In their *humoral pathology*, which dominated the medical thinking during more than a century, Hippocrates (460-377 B.C) and his followers, explained that the brain was made of *moist phlegm* (the other three fluids being yellow bile, black bile, and blood). According to one of their hypotheses, an excess of moist in the brain caused epileptic seizures [37].

The philosopher Plato (428-348 B.C.) had ideas about a divine seed that was placed in the brain, which allowed one to see and hear things and reason about the sensed. This seed was complemented with more animal-like passions, controlling appetites of all kinds (vegetative souls), which were located in the guts, and an elevated superior soul that was situated in the heart. Aristotle (384-322 B.C.) gave the brain the role of a peripheral cooling system that regulated all the heat that was produced by the heart. Rene Descartes (1596-1650 A.D.), who is often blamed for the dualistic split between mind and body, was one of the first to propose a different view. He pictured the human body as an intricate machine made up of small parts, passive in their nature, but somehow winded up by a rational soul that he thought resided in the pineal gland [37].

Many of the early discoveries of the nervous system are attributed to the British physician and pathologist Thomas Willis (1621-1675 A.D.). For many years, he took care of patients on daily rounds in the countryside and at night he dissected corpses with like-minded scholars and natural philosophers at Oxford. Gradually, Willis and his colleagues explored the functional anatomy of the brain and 1664 he published the book *The anatomy of the brain and the nerves*, which was the first book ever to be devoted entirely to the nervous system. Inspired by his clinical work, Willis also made many observations of mental afflictions that nowadays would fall under psychiatric and neurologic diagnoses. Willis was a religious man and kept a belief in a soul alive, and within his functional neuroanatomy, the soul had moved from the heart and up to the brain [37].

The revolutionary idea of evolution by natural selection posed by Charles Darwin (1809-1882), inspired a focus on the function of the mind rather than its structure and opened up the radical thought that we share many of these functions with relatives in the animal kingdom. However, it was not until a few decades into the 19th century, that psychology began to take the form of a field

of its own. The German physician and psychologist Wilhelm Wundt (1832-1920) and the American philosopher and psychologist William James (1842-1910) have both been called *the father of modern psychology*. Both Wundt and James were fond of knowledge gained by *introspection* and thus interested in the study of conscious experience and its various elements [38]. The popularity of the introspective school was about to decline rapidly as the positivistic movement, with its emphasis on objective measurement, paved the way for the *behaviouristic* school of psychology, pioneered by John B. Watson (1878-1958), and further developed by B.F. Skinner (1904-1990) [38].

Grounded in the clinical niche that became *neurology*, the Austrian physician Sigmund Freud (1856-1939) took an interest in cases of hysteria and neuroses [39]. From the careful observation of his patients, he elaborated a whole new theory of mental equilibrium or tension. Freud postulated that mental disorders were the result of unresolved conflict between unconscious animal instincts (especially sexual) and our psyches attempts to tame them to adapt to the prevailing social norms. Freud believed that many of these conflicts were buried in the unconscious in early childhood and he developed a psychotherapeutic method of free-association (psychoanalysis) that could systematically let out the steam from the brewing conflicts within [39].

After the Second World War, clinical psychology was almost exclusively focused on the healing of wounded and distressed minds, and most research concerned pathology and its effective treatment, grounded in basic science where behaviourism was the dominating view. During the 1950s and 60s, a movement was taking form that criticised this view for being narrow-minded and neglecting important facets of human experience, including the more positive features of living a productive and meaningful life. In many ways, this critique of behaviourism and psychoanalytic schools was an echo of the gestalt movements critique of behaviourism, and this new movement, that came to be known as *humanistic psychology*, was inspired by proponents of the gestalt view [39]. Front figures like Abraham Maslow (1908-1970), studied people who excelled in life and proposed a theory of self-actualization, and Carl Rogers (1902-1987), whose work defined the qualities of a psychologically healthy person. Rogers also wrote about the importance of parental acceptance and positive regard for the healthy development of children [40].

In the early 20th century, a movement in Europe reacted to the mechanistic and reductionistic view dominating the medical field, but at the same time allied with the neurologists and psychoanalysts, developed modes of treatment grounded in a holistic view of human beings. This movement was to be called *psychosomatic medicine*, and when a significant proportion of its proponents fled WW-II to the United States, this new branch tried its best to be accepted in mainstream medicine through a more empirical approach and with research-based practices [41].

The discovery of the physiology of adaptation to danger and injury that is the fight and flight reaction to stress is accredited to the Harvard physiologist Walter Cannon (1871-1945). His discoveries were followed by the proposal of a general psychophysiology of “stress,” with neurological, endocrinological and immunological components, pioneered by the Hungarian physician and biochemist Hans Selye (1907-1982). However, the stress theory proposed by Selye was mostly ignored by contemporary colleagues but eventually, his theories took root and became a cornerstone in the psychosomatic movement [41]. We will return to the biology of stress in chapter 21.

9. Psychological Risk Factors and Coronary Heart Disease

During the late 1950s the American cardiologists Meyer Friedman and Ray Rosenman explored the link between stress and heart disease and found that a group of San Francisco accountants showed a dangerous rise in blood pressure and cholesterol during the tax-return season. They were particularly interested in a personality trait characterized by impatience, ambitions, and perfectionism that they called *Type-A behaviours*. They conducted larger trials that showed significant links between Type-A behaviour and CHD, and a review published 1981, by the US National Heart and Lung and Blood Institute, concluded that Type-A behaviour was an independent risk factor [41].

According to historian Anne Harrington, the public acceptance of this link between stress, in terms of competitiveness, and heart disease sparked a thriving relaxation industry with biofeedback and relaxation techniques as bestselling solutions [41]. The solid link between Type-A behaviours and CHD was suddenly becoming significantly weaker in 1988 when Ragland and Brand published a long-time 8,5-year follow-up on the Friedman and Rosenman's population. This longitudinal analysis showed that subjects with Type-A-traits paradoxically had a lower cardiovascular risk [42]. A meta-analysis, summarizing all studies up to 1998 found no evidence for an association between Type-A traits and CHD [43].

A NOTE ON THE EPIDEMIOLOGICAL CHALLENGE OF SOCIETAL CHANGE AND CHD

In the previous chapters, we have seen that many traditional risk factors fall under the term *health behaviours* (e.g., smoking, physical activity, diet and weight and alcohol consumption). The interplay of psychosocial factors, health behaviours and CHD, is incredibly complex. When strong currents of societal change occur over time, it becomes even harder to make sense of the epidemiological data. This challenge might explain the curious disappearance of a strong link between Type-A-behaviour and CHD, that was observed during the second half of the 19th century. When this link was first observed at the end of the first half of the century, we had a society where the behavioural risk factors for obesity, smoking, and stress were more prevalent among those with high SES. At the same time, those with low SES were less sedentary, smoked less and were not over-eating to the same extent. This might partly explain why CHD was more common among the affluent at this time. During the second half of the century, alongside dramatic economic progress, those with low SES changed their health behaviours for the worse, while those with high SES improved their health behaviours, and CHD became a disease of the underprivileged [44].

This complexity highlights both the challenges of the epidemiology of CHD and the need for an enlightened and nuanced view of how social- psychological- and biological factors interact over time. Furthermore, the sum of this introduction shows that we need more knowledge about psychobiological pathways so that theorists can connect the dots of interdisciplinary data into a more coherent picture.

A NOTE ON SOCIAL CONTEXT AND CORONARY HEART DISEASE

Although this thesis is focused on the psychobiology of CHD, in a broad sense, the findings could have implications for theories about how social factors find its way under the skin to influence disease processes [45]. From a philosophical point of view, social factors could interact with and catalyse the effect of psychological factors on health (e.g., cheerful mood could lead to increased social support, that in turn influence biological systems through an implicit sense of safety). However, in most theoretical models, social factors are viewed as more distal to the biological disease processes, than the psychological [45]. Social factors are not investigated directly in any of

the included studies and are therefore presented very briefly here to provide context for a later discussion about the relevance of the results.

The interest in social factors, as determinants of CHD, can be traced back to a second reaction to the common notion that stress was toxic and that people broke down under the pressures of modern life. After the initial hype of Type-A behaviours and various ways to come to terms with these, researchers started to wonder if it might not be the lack of close connections to family, friends and the community, that robbed us of a sense of belonging and wholeness [41]. In a 1979 study, Berkman et al. analysed data collected in 1965-1974, and showed that those who had reported the fewest social ties were three times as likely to be dead nine years later, compared to those with most social relations [46]. During the forty years that have passed, a large amount of data have confirmed that low levels of social support are associated with worse health outcome, while high levels of social support have been shown to promote both psychological and physical well-being. Social support could be further stratified into *social network*, *social resources* and *perceived support* or *closeness of intimate relationships*. All of these facets of social context have been linked to increased mortality in CHD populations [47]. Evidence for the role of social support also comes from correlational studies, which have suggested that social isolation is associated with biomarkers of inflammation (such as CRP and IL-6) [48]. Brown et al. have recently reviewed the literature on loneliness and stress-reactivity, investigated through laboratory stress-test paradigm, and found evidence that supports a link between the two, and suggests that heightened vulnerability to stress could be one of the mechanisms linking loneliness to a worse health outcome [49].

The human brain seems to be especially sensitive to social influences. Studies of neuroplasticity, have shown that several sectors of the growing amygdala grow from the experience of moderate to severe stress, while structures like the hippocampus (important for memory), and prefrontal cortex tend to shrink. These observations come from fMRI studies with physically abused children that have shown that these structural and functional changes are correlated with poorer academic and family functioning [50]. Miller et al. have also shown that low early life social class could leave a biological footprint expressed in adults as altered cortisol signalling and dysregulated inflammatory gene activity [51].

A related determinant, with both social and environmental facets, with implications for CHD, is *work stress*. An extensive body of evidence have linked work stress to both conventional risk factors and to incidence in CHD. In a 2008 publication from the Whitehall II-cohort of British civil servants, Chandola et al. reported data from 10308 participants, aged 35-55. The authors showed that exposure to work-stress was related to CHD incidence, metabolic syndrome, heart-rate variability (HRV) – a measure of ANS-regulation in which low variability reflects sympathetic over-activity – and morning cortisol. Interestingly, the connection between work-stress and CHD incidence was strongest under 50 years of age (RR 1.68 CI 1.17-2.42) [52].

Basic knowledge of the cultural and historical history of the study of psychosocial variables and CHD is vital for at least three reasons. Firstly, it will become apparent that the treatment modalities (e.g., relaxation training and stress reduction courses) that were used in the first landmark trials were influenced by trends in both the scientific field of psychosomatic medicine and in society at large. Secondly, knowledge about how recent in time the first studies of psychological phenomena in the context of cardiology were done, can inform our rationale for a continuation of the exploration of these questions. Thirdly, our theories and models for how psychological states or traits translate into disease processes in the coronary arteries are firmly built on discoveries about the psychobiology of stress and early conceptualizations of vulnerabilities and coping abilities.

10. A Brief History of Depression and Depressive Symptoms

Depression and symptoms of depression will be introduced in a broader and deeper manner than other psychological risk factors. The explanation for this is multifaceted. Firstly, *depressive symptoms* is the only psychological variable that is used as an outcome measure or selection criteria, in all four studies. It could be argued that the broad concept of *depressive symptoms* is a phenomenon distinct from the disorder *depression*. Even though researchers often use different instruments to capture these phenomena, many thinkers have argued that the construct of *depressiveness* covers a continuum from well-being to disabling disorder, and thus depression represents one of the far ends on the spectrum [53,54]. Secondly, depressive symptoms are surprisingly common among CHD patients. Thirdly, depressive symptoms covers a broad variety of symptoms of psychosocial distress, including low mood, anxiety, irritability, fatigue, sleep-difficulties, meaninglessness, etc., and may represent a continuum from well-being to depression as a severe disorder

The illness we call depression has probably been torturing unfortunate individual human beings since the first members of our species began to inhabit the African savannah some 200000 - 300000 years ago. In historical time, the first clear description of the diagnosis is attributed to Hippocrates. In his famous *Aphorisms*, he used the term *melancholia*, to describe a syndrome of fear and sadness that lasts a long time, which also is accompanied with an aversion to food, despondency, sleeplessness, irritability and restlessness [55]. Melancholia was thought to be the result of an excess of *black bile*, which in turn could be caused by an unbalanced relationship between the body and its surroundings (including diet, living conditions and atmospheric conditions). It is highly relevant to note that Hippocrates wrote of the importance of distinguishing between depression as a disorder, and normal variants of deep sadness or fear, which could present similar symptomatology. Hippocrates and his followers understood that a correct diagnosis required that the physician also included a careful analysis of the context of the presenting symptoms. Symptoms stemming from severe losses, complex and stressful life situations and romantic disappointments that were proportional to these contexts were thus considered normal reactions. Hippocrates also noticed that a longer duration than expected could point in the direction of a disorder. This, rather self-evidently wise approach to the diagnostic procedure, as well as the Hippocratic list of diagnostic criteria, were remarkably conserved during the two centuries that followed [55].

Thomas Willis, who saw his patients in the rural area around Oxford, noted that the inner darkness of melancholia resulted in a distorted image of the outside world, and if the brain was diseased enough, the rational soul could become permanently affected. The advice he gave his depressed patients was to engage in pleasant conversation and activities, including creative activities (jesting, singing, painting etc.) and to go fishing. Willis viewed these activities as a kind of mechanical cure that directed the pieces of the rational soul back into their proper circuits in the brain. He frequently complemented these early forms of “behavioural activation” with a unique blend of steel syrup that he thought could wash out corpuscles of salt and sulphur from the blood [37].

The science of the nervous system and the idea that melancholia could be a disturbance of the brain resulted in a split in the nomenclature. The first type was a severe form of the disorder, one that we today would call major depressive disorder (MDD), and was usually taken care of by special healers for the insane. The second type was called *nervous disorder* and was taken care of by general physicians and early neurologists. This second type, characterized by anxiety, fatigue, obsessions and somatic pre-occupations, was later labelled *neurosis* or *neurasthenia*. Pioneers in the field that soon would be called psychiatry, like Emil Kraepelin (1856-1926) and Sigmund Freud (1856-1939), were relating to these two subtypes in their writing, and none of them seem to have opposed themselves to the critical distinction between normal distress and symptoms of a disorder [55].

11. The Diagnosis and Classification of Depression

When the three parallel scientific fields of neurology, psychiatry, and psychology, were addressing the many unanswered questions surrounding the two kinds of depression syndromes, the result was an increase in confusion rather than a gradual clarification. In 1979, the year the author of this dissertation was born and one year before the third edition of the DSM-manual was published, two prominent psychiatric researchers wrote a review of the literature and called the state of knowledge “*a hodgepodge of competing and overlapping research of depression*” [55].

The scientific and clinical mess of a few hundred years of empiric exploration was transformed into a relative uniformity and simplicity when the DSM-3 came out. The DMS-3 abandoned the distinction of *primary depression* (disorder) from *secondary* (dependent on pre-existing disease or contextual factor). The only remnant exemption was if the symptoms were due to bereavement. This bereavement-exemption, the last straw from the Hippocratic contextual approach, was abandoned in the fifth version of the DSM-criteria (2013), representing a break with a 2500-year tradition. In a strict sense, it is nowadays no longer possible to be devastated by loss or trauma with preserved normalcy and health [56].

The rewards for a binary classification of depression, which mimics the categorization of somatic diseases, have streamlined clinical research and terminology that transcend different schools of thought in clinical psychology. But these rewards have not come without costs. In addition to the tendency to medicalize normal facets of the human predicament, and thus provide a rationale for the idea that psychological suffering should be treated away, it also contributes to a heightened risk of underestimating the need for support or treatment among patients with subclinical levels of distress.

The simple case-or-not case-model of depression has been criticised for applying a binary categorization to a phenomenon that is fundamentally continuously distributed in the population [53]. Opponents to the binary classification have advocated a more dimensional approach, where the continuum from full health to severe disability is recognized [57]. A solution to this dilemma, a kind of middle-way between simplification and confusion, is a *graded* or *staged* model of depression. Proponents of a staging model argue that one of its advantages is that it provides a sharper tool to select appropriate interventions, and also contribute to a more clever distribution of limited health-care resources [53].

The Harvard University psychiatrist Vikram Patel has recently proposed a four-stage model of the depression syndrome, spanning from *wellness*, through *distress*, *disorder*, and all the way to *recurrent* or *refractory major depression* [53]. He argues that the strength of this model is that interventions can be graded, delivered from diversified platforms, and consist of different modalities of treatment; from primary preventive mental health practices in the community at the wellness stage to combinations of antidepressant treatments and inpatient care for recurrent major depression. A table of Patel’s four-stage-model can be viewed in Appendix B.

12. The Biology of Depression

Developing increasingly powerful tools to probe deeper down in biological systems have to date been a recipe for success in medical research. However, when scientists have tried to copy this strategy for the disorder of depression, the results have not only been clarity, deeper insight and new ideas for treatments but also increased confusion from the stunning complexity found.

Krishnan and Nestler addressed this complexity in their 2010 review called “*Linking molecules to mood*,” and stated:

“Major depressive disorder is a heritable psychiatric syndrome that appears to be associated with subtle cellular and molecular alterations in a complex neural network. The affected brain regions display dynamic neuroplastic adaptations to endocrine and immunologic stimuli arising from both within and outside of CNS. [] Current psychopharmacological antidepressant treatments improve depressive symptoms through complex mechanisms that are themselves incompletely understood” (p.1305) [58].

Without losing ourselves in the details of the incompletely understood biology of depression, a few important hypothesis and findings could be relevant to review for our coming discussion of the links between psychological resources and risk factors and CHD. It should also be noted that *Study III* and *IV* in this thesis included patients with depressive symptoms in the range of mild to moderate depression. Furthermore, since most biological mechanistic studies have been made on patients with MDD, it is not entirely clear if the biology of depressive symptoms represents a less severe version of the biology of MDD.

The so-called “*monoamine hypothesis*” stipulates that dysregulated levels of neurotransmitter substances from the family of monoamines, including 5-HT (5-hydroxytryptamine, or serotonin, or SE), noradrenaline (NA) and dopamine (DA), is the molecular basis for depression. Early evidence came from observations that depressed patients had lower levels of metabolites from these neurotransmitters and from the fact that antidepressants like the tricyclic antidepressants (TCAs) and the SSRIs, that increase the levels of these monoamines, were effective. During the last two decades this hypothesis has been proved to be incomplete in its own, and although the monoamines are important factors, they seem to play integral roles in a more extensive and much more complex web of interrelated mechanisms [59].

The psychobiology of *the general stress-response* has for long been implicated in the biology of depression. This hypothesis has gained support from strong connections between stressful experiences and subsequent episodes of depression in vulnerable people. Although somewhat inconsistent, alternations in the hypothalamic-pituitary-axis (HPA), including hypersecretion of corticotrophin-releasing hormone (CRH) from the hypothalamus, impaired negative feedback to the central parts of the axis, enlarged adrenal glands, and chronic hypersecretion of the hormone cortisol from the adrenal cortex [59]. Since the biology of stress is of pivotal theoretical relevance for all studies in this thesis, a more detailed introduction will be presented in chapter 21

Inflammation, both elsewhere in the body and the central nervous system (CNS), has become a hot topic in depression research during the last decade. The hypothesis that dysregulated inflammatory activity could cause depression is based on findings that depressed people have higher levels of the circulating inflammatory cytokines IL-1 β , IL-2 IL-6 and tumour necrosis factor- α , (TNF- α), as well as the acute phase protein C-reactive Protein (CRP) [59]. Since psychological stress is known to lead to increased inflammation, a positive feedback loop could occur. Since inflammation is a proven pathway in atherosclerosis development, and maybe also an essential process in depression,

some authors have suggested that this is the primary link between the two disease processes. Poole et al. have even suggested that depressive symptoms in CHD patients might be qualitatively distinct from psychiatric populations, and that the central explanation for their depressiveness is the increased inflammation in the vascular tree, which produce so-called *sickness behaviour* through specific effects in the CNS [60].

Patients with depression have lower levels of a *neurogenesis* (the growth of new neurons) stimulating peptide named brain-derived neurotrophic factor (BDNF). Furthermore, the effects from SSRIs may partly come from stimulating neurogenesis in areas important for depressive symptoms such as prefrontal cortex, hippocampus, and amygdala [59].

In a recent review article, Dean and Keshavan, highlight that all proposed mechanisms are reciprocally interconnected, and all of them could lead to alterations in other. For a person with low distress tolerance, a stimulus that is perceived as stressful could orchestrate a series of interconnected and mutually enhanced, a top-down cascade of processes in the whole psychobiological system [59]. On the other hand, any primary biological alteration could impair emotional regulation and critical cognitive processes, and through a bottom-up cascade of interconnected processes, overwhelm the individual at the psychological level. Ultimately, more often than not, dysfunction is derived from both top-down and bottom-up influences, since the two levels are impacting each other bi-directionally. Depression becomes the final common pathway [59]

This integrative view is in line with findings from the search for the *depression gene*. In a 2010 review article, Lohoff, summarize the results from family-, twin- and adoption studies, as well as genome-wide association studies, and concludes that no single genetic variation has been identified to increase the risk of depression substantially [61]. Instead, the author concludes that there are more likely to be multiple genetic factors that interact with environmental factors in the development of depression. Gandal et al. have recently showed that there were distinct patterns of gene-expression perturbations, measured by *transcriptomic profiling*, that were linked to single nucleotide polymorphisms [62]. The analysis was based on genetic tests of 900 cortical samples from deceased patients with autism, schizophrenia, bipolar disorder, depression, and alcoholism. Interestingly, the pattern of abnormal gene-expression was shared across these different disorders and not specific to anyone.

Another recent review article adds other biological factors that could influence the six described above. Akil et al. complemented the list with a suggestion that *circadian disruption* (e.g., sleep difficulties, interact with brain circuits and ANS), *mitochondrial function* (e.g., metabolism of calcium and free radical damage) and *peripheral organ function* (e.g., the cardiovascular system, immune system), all could play significant roles [63]. Furthermore, Akil et al. highlight that psychosocial and environmental factors, such as childhood adversity and poverty, can interact with all other factors, and that sex differences could influence mechanisms on many different levels.

A NOTE ON THE EVOLUTION OF DEPRESSIVE SYMPTOMS

Even though the field of biology never became quite the same since Charles Darwin published his *On the origin of species*, in 1859, the science of psychology was somewhat slow to adapt to this disrupted view of the human organism. The addition of an evolutionary and historical perspective can shed some light on the grand and complex questions about *why* we humans behave as we do, even though hypotheses that are grounded in historical facts are difficult to test. Anyhow, the alternative story of creation, offered by archaeology and evolutionary genetics has inspired some thinkers to speculate about an evolutionary origin of depression [64].

The psychiatrist Randolph Nesse argued that there are good reasons to think that mild states of low mood could have adaptive functions in specific contexts [65]. He argued that a better understanding of the normal function of low mood could be the missing piece in our understanding of depression. Nesse proposed that when an individual is unable to find a way to reach a crucial goal to his or her core meaning in life, then efforts in all other domains in life would be poorly spent. For such an individual it would be better to pull back and consider different routes to the goal or give it up entirely. Nesse used physical pain as a compelling analogy, echoing the contextual view of Hippocrates. The capacity to feel pain is normal and useful and those who are lacking it die young. Chronic pain is abnormal and devastating for patients. Depression is mental pain that is useful in general and in some contexts, but debilitating in excess and when chronic. Other theories have focused on the socially adaptive functions of the symptoms of depression, including the hypothesis that they represent *submissiveness signals* to the social environment following unsuccessful attempts at rising in the ranks, and thus contribute to the maintenance of important social ties [66].

A third hypothesis, which is especially relevant for our exploration of psychological risk factors and resources and CHD, is the *infection defence hypothesis* of depression by Anders et al. [67]. The authors cite recent findings of the bidirectional pathways of communication between the nervous- and immune systems and that heightened states of inflammation create a collection of psychological states, called *sickness behaviour* that has many of its features in common with symptoms of depression. According to Anders et al. mood is a subjective experience that could coordinate and orchestrate a wide array of physical and behavioural responses.

Anders et al. highlighted the enormous influence of infectious diseases during the evolutionary history and conclude that sickness behaviour and the cluster of symptoms called *depression*, could have increased survival and reproduction by prompting infected individual to withdrawal from the social context and conserve energy for fighting off the infection. These behaviours could also avoid the spread of the disease to kin and avoid meeting additional pathogens [67]. This hypothesis could explain why depressive symptoms are both common and heritable and it provides another argument for the investigation of inflammation as an underlying mechanism in depression. It also takes in the broader context of underlying problems such as stress, sedentary lifestyle, poor diet and sleep disturbances, and as such it provides a bigger picture in which our efforts to understand the relationship between psychological factors and CHD could contribute with valuable insights.

13. The Global Burden of Depression

When the predicament of the human species is viewed through a historical lens, it has been argued that we are currently in the middle of a dramatic shift in what our most significant challenges are and how we die. According to historian Yuval Noah Harari, we are for the first time in the history of humanity, more likely to die from over-eating than starving, succumbing from disorders of old age rather than an epidemic infectious disease, and we are more likely to kill ourselves than to be killed by a fellow human being [68]. This trend on the large scale does not imply that the burden of famines, infections, and wars are not still serious and very tragic parts of many people's lives, but for the human species as a whole, it represents a piece of good news that may not taste very good once chewed for a while. It is simultaneously ironic and tragic that we have used our large and ingenious frontal-lobe-derived cognitive capacities to figure out ways to prevent famines, armed conflicts, and epidemics, but also rendering many of us too sick, too stressed, too lonely or too depressed to enjoy the hard-won security and comfort.

On a global scale, resources for addressing this gargantuan health issue have seldom had the highest priority. Developing countries often prioritize infectious diseases, maternal- and child health, and developed countries have focused much of their resources to combat cancer and heart disease. Important changes are currently happening as the contribution of mental health disorders to the global burden of disease and disability has been increasingly recognized during the last decade [69,70]. In the 2005 report of global disability, WHO concluded that 32 % of all years lived with disability (YLWD) were due to mental health disorders, including depression (12 %), alcohol dependence (3 %), schizophrenia (3 %), bipolar disease (2.5 %) and dementia (1.5 %) [71].

According to WHO, more than 300 million people on this planet suffer from depression this very moment, with women consistently more affected than men. The estimated annual deaths from mental health disorders are 1.2 million, but this number does not include suicides (which are categorized as *intentional injury*). Suicide is often, but not always, the worst down-stream consequence of depression, and it is the second leading cause of death in the group of 15-29 years old [71]. Every year, close to 800 000 people die from suicide, but official data from low- and middle-income areas of the world have been shown to misrepresent the actual numbers [71].

In Sweden, the prevalence of depressive disorders (from mild to major) has been shown to be around 17 %, with a point prevalence of MDD of 5 % [72]. These estimates come from a survey of 3001 randomly selected adults, and thus do not include children and youths. The study used Patients Health Questionnaire (PHQ)-9 and the content, and the cut-off logarithm is derived from the *Diagnostic and Statistical Manual of Mental Disorders* (DSM).

From these numbers, we can notice that depression, like CHD, is a major source of suffering, disability, and death on a global and national scale. From a theoretical and empirical point of view, we also have reasons to believe that subclinical levels of depressive symptoms might be affecting an even larger proportion of the human population than the diagnosable disorder of depression. Although the health consequences of subclinical symptoms may be less grave, they have been proven to influence disease risk in a dose-response manner [73] and since the proportion of CHD patients suffering from depressive symptoms, they represent a significant clinical problem. The recognition of this problem has been quite extensive in the scientific community but there is still a considerable gap between what has been explored in studies and the care that CHD patients receive in clinical practice. The studies in this thesis aim at filling this gap with a few pieces of knowledge to the larger puzzle about the role of psychological variables in CHD.

14. The Assessment of Depressive Symptoms

In studies that aim to correctly diagnose cases of depression, e.g., for the inclusion of a group of patients to an intervention study, often use a combination of clinical interview and a structured interview schedule. However, when researchers want to study the prevalence of depressive symptoms, e.g., in larger cohorts and epidemiological studies, the more practical and cost-saving method of self-report instruments is most common [74].

In all studies of this thesis, the instrument *Centre for Epidemiological Studies Depression-scale* (CES-D) was been used, either as an outcome measure or as a screening and selection tool. The CES-D scale was developed by Leonore Radloff (1935-2016) and her colleagues during the second half of the 1970s [75]. Along with fundamental psychometric properties, the scale was published in 1977, which we might remember was at the end of the era of diverse and disparate research on the topic depression. It was also two years before the launch of DSM-III and its MDD-criteria that would dominate the field.

Radloff, who was working at the Centre for Epidemiologic Studies at the National Institute of Mental Health in Bethesda, Maryland, USA, had set out to create an instrument for the measurement of depressive symptoms of the general population. In this regard, the CES-D was different from most other scales, which aimed at diagnosing patients with depression or evaluate symptom severity over time. Radloff borrowed items from previously validated depression scales and constructed a 20-item questionnaire that focused mostly on the affective component of depressed mood. Also, a few items of feelings of guilt, worthlessness, and hopelessness, as well as loss of appetite and sleeplessness, were included. She also added four positive items to break tendencies of response set, but also to measure positive affect or their absence [75]. The items, their content and their anchors, of the CES-D-scale, could be read in Appendix A.

In the 1977-article, Radloff made very clear that it was not intended as a diagnostic tool. However, that did not mean that future users would give it a try. In 1997, Beekman et al. tested the criterion validity of CES-D, which is its ability to correctly diagnose depression, among 487 older adults still living in the community [76]. They compared CES-D scores with the diagnosis of MDD through the structured Diagnostic Interview Schedule (DIS), which work through the DSM-criteria. They found that the sensitivity was 100 % and the specificity was 88 %, and the positive predictive value was 13.2 %. Furthermore, they found that false positives were not more often found among elderly with a somatic disease, cognitive impairment or high anxiety, compared to a normal population.

Other studies have shown good sensitivity, but meagre specificity. In a psychometric evaluation of mothers to chronically ill children, the total score was almost equally influenced by symptoms of anxiety [77]. In a recent meta-analysis evaluation of depression diagnostic instruments, Pettersson et al. concluded that CES-D had a sensitivity of 95 % and specificity between 33 % and 73 %, depending on context. In the majority of studies of the impact depressive symptoms have on CHD incidence and mortality, other more diagnostically oriented scales have been used, including; Beck Depression Inventory (BDI); Hospital Anxiety and Depression scale (HAD); PHQ-9; the Structured Clinical Interview (SCID) or the DIS-interview. However, in the more recent CARDIA-study, CES-D was used as an outcome measure [78]. Furthermore, Blumenthal et al. studied the CES-D scores of 817 patients undergoing CABG [79].

15. Depressive Symptoms and Coronary Heart Disease

The link between depression and heart disease was first spurring scientific interest in the 1930s [80]. However, it was not until 1987, when the Danish psychiatrist Anita Weeke published a longitudinal study of 8136 patients with manic depression, followed for an average of four years, that empirical data were beginning to surface. The study showed that the patients died of cardiovascular disease to a larger extent than expected [81]. Weeke et al. believed that the treatment for depression could explain the link. During the three decades that followed, a large body of data has established depression as a strong predictor of cardiovascular disease, but the debate over whether there is a *causal* link, or if another factor explains the apparent connection, is not resolved to this day [82,83].

Thombs et al. published a comprehensive literature review of depression in myocardial infarction survivors in 2006 [84]. Their analysis showed that major depression was identified in almost 20 % of patients with newly diagnosed CHD (pooled data from 10785 participants) and significant depressive symptoms, corresponding cut-offs for mild depression, was found among 15-30 % of patients depending on assessment tool used. In a more recent meta-analysis of prevalence studies of MDD and CHD patients, Shanmugasagaram et al. pooled data from 8 studies and found that MDD was present among 19 % of women and 12 % of men [85].

For an extended period, it was unclear if depressive symptoms among CHD patients made any difference for prognosis and subsequent disease or death. This question has more or less been settled by handful of large prospective trials that have proved the following:

- + In otherwise healthy people, subclinical depressive symptoms are associated with significantly increased risk of developing CHD [73].
- + Patients with major depressive disorder (MDD) are more likely to have both fatal- and non-fatal myocardial infarctions compared to patients without depression [86].
- + In patients hospitalized for myocardial infarction (MI), those with MDD apparent before the MI had more complications during their hospitalization [87].
- + In patients with established heart disease, depression represents a significant independent risk factor for mortality and morbidity, and patients with depressive symptoms have been shown to have *twice* the risk of dying during the following two years after a coronary event [88,89].

Since many studies of the link have been cross-sectional, or longitudinal observations of patients with existent symptoms or disease, conclusions about causality have been lacking. In a study of 10036 British civil servants, symptoms of depression were measured prospectively at six different points in time during 24 years. When incidence in CHD was studied in this cohort, the investigators showed that depressive symptoms increased the risk of CHD in a dose-response manner, but they found no evidence for reversed causation [90].

A recent study of a Swedish population of almost 15000 patients with stable CHD, with a follow-up time of 3.7 years, showed that depressive symptoms were associated with increased risk of a composite CVD-endpoint (including cardiovascular mortality and non-fatal MI or stroke), (HR 1.21, CI 1.09-1.34)[91].

Data, pointing in the same direction, came from two clinical trials with other risk factors as an outcome. In the Coronary Artery Disease Development in Young Adults (CARDIA) trial, researchers showed that depressive symptoms were associated with greater increase in the CHD risk factor Body Mass Index (BMI) over time, but higher BMI at baseline was not associated with the subsequent development of depressive symptoms [78]. In the COPE-trial, authors reported that severity of depressive symptoms predicted the decline in C-Reactive Protein (CRP) between one and three months, but not vice versa [92].

Early studies of the persistent depressive symptoms among CHD patients provided inconsistent results [93,94]. Researchers still debate over if depressive symptoms represent a natural response to the distressing experience of having a coronary event, and thus improve spontaneously over time, or if the symptoms were present before the event and persists long after the initial crisis has been resolved. This question has evaded clarity for a number of reasons. Firstly, researchers have used different screening and outcome measures of depressive symptoms and with different cut-offs. Secondly, studies have been carried out on different type of populations with a variety of follow-up times. In a 2006-review from Thombs et al., cited above, conclusions about persistence were avoided since follow-up times varied considerably in the studies. However, the authors concluded that a significant proportion of patients continue to be depressed in the years following discharge [84].

Since 2006 many studies have addressed this knowledge gap and added essential findings of what persistent symptoms mean for the risk of future CHD events. At least two different studies have shown that patients who show depressive symptoms with newly onset after the CHD event, had a higher risk of further CHD events or death, compared to patients with symptoms that were prevalent before the first event [95,96].

A 2011 study of 667 CHD patients, followed over five years, showed that 20 % of the patients had persistent depressive symptoms when assessed two and five years after the event [97], extending on earlier findings from similar studies with 12-month follow-up [98,99]. Furthermore, in one of the clinical trials of SSRI, researchers showed that baseline severity of depressive symptoms and failure to improve during the first six months were strongly related to CHD mortality the following seven years [100]. In a five-year follow-up study of 489 MI-patients, Parker et al. showed that historical or transient depressive symptoms did not result in heightened CHD mortality risk, but persistent and existent depressive symptoms did [95].

The issues of prevalence and persistence have theoretical implications for all studies in this thesis and practical consequences for *Study III* and *Study IV*. In the first two studies, depressive symptoms were measured at baseline and then studied incidence in CHD during the following eight years. In *Study III* and *IV*, patients were screened one month after their first coronary event, and they began an intervention within a year of their event. Depressive symptoms were also measured immediately after the intervention and 12 months later.

16. The Treatment of Depression

As we saw in chapter 11, the characterization of the melancholic or depressive disorder has been surprisingly stable during the last 2000 years. However, the various prescriptions of its cure have been uttermost diverse. Galen advised bloodletting, but many of his successors used this treatment only for the most severe cases and were more in favour of purgation as a mean to restore the humoral balance. Along with the stimulation of menstrual- and haemorrhoidal blood-flow, these treatments remained popular into the early enlightenment when Thomas Willis began treating his melancholic patients with steel-syrup and behavioural activation. In fact, the standard treatment during the first and second century was often accompanied by detailed advice about diet, warm baths, pleasant social company and sleep hygiene [101].

Although different views of the disease mechanisms came and went during the 17th and 18th centuries, it was not until the turn of the 19th century that new treatment modalities saw the light of the day. The French physician Philippe Pinel (1745-1846) took a firm stance against all medical remedies for melancholia and instead advocated changes in the patient's outer environment to stimulate a shift in attitude (also known as Pinel's *moral therapy*). During this era, opium had a couple of decades of popularity as a sleep medication and general anxiolytic agent but was later abandoned [101].

At the beginning of the 20th century, the highly influential German psychiatrist Emile Kraepelin (1856-1926) recommended a *rest cure*, which often meant removal of the patient from the environment that had made him or her sick. From the 1930s the scene became increasingly complex when different schools of the newly founded scientific discipline of psychology came up with their brand of talking cure, e.g., Freud's psychoanalysis. During a short period, some patients with particularly severe symptoms got some of their over-active limbic structures in the brain removed by a stainless steel spoon, in the procedure known as lobotomy [101].

According to *psychodynamic theories*, which go back to Sigmund Freud and his followers, depression was the result of unresolved inner conflicts, especially the loss of an ideal representation of the self. The psychodynamic theory provides the basis for psychodynamic therapy (PDT) [38].

Behaviouristic theories explain the causes of depression in terms of learning, or reinforcement patterns, stemming from models of operant conditioning. According to this theory, people respond to a lack of positive reinforcement, e.g., from pleasant activities and relationships, with corresponding low mood and depressive behaviours. In some contexts, social withdrawal could also become negatively reinforced, creating a negative spiral. The behaviourally oriented theories provide the basis for both behaviour activation and as one of the components of cognitive behavioural therapy (CBT) [102].

According to Aaron Beck and his colleagues, some individuals have *cognitive schemata* that colour their interpretation of both small and large events in everyday life in a negative frame, which results in cognitive, affective, motivational and behavioural consequences. The critical process in this theory is the *biased content of thought*, which stems from erroneous assumptions. The cognitive theories of depression provide the theoretical basis for cognitive therapy and CBT [102].

The *attachment theory* stipulates that depressive symptoms come from the loss of secure bonds to significant others, which typically lead to feelings of distress and anxiety. If prolonged, this lack of a sense of safety, leads to dejection and hopelessness [58]. Attachment theory was one of the influencing theories when the interpersonal psychotherapy treatment (IPT) protocol was developed. IPT was also influenced by interpersonal communication theories, and the format was much

inspired by CBT and PDT. According to IPT, depression results from events in the psychosocial environment, like losses, conflicts, role transitions, etc. These events have a strong influence on mood and psychosocial functioning, which further worsen the situation in a downward spiral [102].

During the mid 19th century, the world of psychiatry received the first antipsychotic drug *torazine* (1952), and soon it also got *lithium* and *benzodiazepines* as tranquilizers. These drugs were sometimes used for depressed patients, mainly when there were comorbidities, but it was not until the 1980s that depression got its pill-cure [101].

The story about the enormous early success of selective serotonin re-uptake inhibitors (SSRIs), followed by several setbacks, is beyond the scope of this introduction. However, it could be mentioned that one year after the American Food and Drug Administration (FDA) had approved the first SSRI, *fluoxetine* (also known as *Prozac*), almost 2.5 million prescriptions had been written, and in 2002, the number of prescriptions had raised to more than 33 million [103]. Since these early days, SSRIs have been increasingly criticized, but continue to be the most common medication prescribed for depression.

In 1997, alarming studies were published, which showed that more than 75 % of the effects of SSRI-drugs were derived from the placebo effect. A follow-up analysis, with both recent trials and exclusively based on the most rigorously conducted studies, showed that in patients with mild to moderate depression, the benefit of SSRI was small, or even negligible. Patients with MDD, however, had substantial benefits from the medication compared to placebo [103]. In a recent meta-analysis, which included 131 RCTs, Jacobssen et al. concluded, while there was a substantial risk of bias in most trials, SSRIs might have a statistically significant effect, but the clinical significance seems questionable, and the potential small beneficial effect seem to be outweighed by harmful side-effects [104].

This interpretation of the overall evidence was challenged in a more recent meta-analysis. Cipriane et al. conducted a network meta-analysis of 522 trials, pooling results from a total of 116477 participants, and found that all common SSRIs were indeed more effective than placebo, with ORs ranging between 1.37-2.13 [105]. In the comparison among different SSRIs, *mirtazapine* was the second most effective, *sertraline* was no. 10 out of 21. When it came to acceptability (measured as dropout rate) the two drugs were no. 9 and no.11 out of 21, respectively. The curious reader might ask how *fluoxetine* (*Prozac*), performed. It was no. 16 in efficacy, and second best in acceptability [105].

PHARMACOLOGICAL TREATMENT OF DEPRESSION IN CORONARY HEART DISEASE

There is an intriguing convergence in time between when the link between depression and CHD became known, and the availability of a somewhat hyped pharmacological treatment for depression. One can only imagine the excitement that sparked in the air when cardiologists and psychiatrist discussed this overlap in research ambitions. However, large clinical trials take time to plan, fund, launch, and report in peer-reviewed journals, and the field of medicine would have to wait until the new millennium before the first trials of SSRIs for depressed CHD patients were published. The early studies were focused on safety and efficacy, but subsequent trials aimed at finding out if the treatment of depression could influence incidence in CHD.

In the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART), Glassman et al. published results from a multi-centre and double blind study of the SSRI *sertraline* (Zoloft) for depressive symptoms in CHD patients [106]. Between 1997 and 2001, 369 patients from the USA, Europe, Canada, and Australia, with first time acute myocardial infarction or newly diagnosed

unstable angina pectoris, were randomized to get either the antidepressant or placebo. The drugs were prescribed in flexible doses and for a total of 24 weeks. To be included in the trial, the patients had to have MDD, diagnosed with the 17-item Hamilton Depression Rating, and not having any other life-threatening illness. The primary outcome was a proxy measure of the heart's capacity to pump out blood to the rest of the body with efficiency (left ventricular ejection fraction, LVEF), and depressive symptoms were on the list of secondary outcome measures.

The results must have been disheartening for all involved. Sertraline had neither an effect on the primary outcome LVEF nor on any other CHD risk factor measured. When scores of depression were compared for the two populations, there were no benefits in the SSRI-group. However, when the two groups were further divided, analyses showed that those who had previous episodes of MDD, and those with severe symptoms, had a small but statistically significant benefit compared to placebo. The SADHART-group followed their cohort for seven years and in 2009 they reported their main findings. Twenty-one percent of the patients had died, and analyses of the prospective data showed that neither previous episodes of MDD, nor onset before or after the index event was associated with any increase in mortality risk. Furthermore, the 24-week treatment with Sertraline did not seem to make any difference for long-term mortality. However, the baseline severity of depressive symptoms and failure to improve during the 24 weeks were strongly connected to increased mortality. The authors also observed that patients who improved significantly were better adhering to medication regimens than those who did not [100].

In 2003, results from the ENRICHED-trial were published. The aim was to study reductions in mortality or recurrent MI in a group of 2481 CHD patients. Subjects were randomized to either usual care, or to an intervention consisting of Cognitive Behavioural Therapy (CBT), with the addition of *sertraline* if symptoms were judged to be severe [107]. The results were very similar to SADHART; the treatment arm responded with modest improvements in depressive symptoms, but there was no apparent effect on event-free survival. The authors explain the small effect partly by the significant spontaneous recovery in the usual-care group, but one of the authors has confessed that the outcome was a major disappointment [41].

In 2007, Honig et al. conducted a trial with similar design and size as the SADHART, but with the drug *mirtazapine* (Mirtazapine). In a prospective multi-centre study, the researchers screened 2177 patients for depressive symptoms and included 91 that fulfilled inclusion criteria. Included patients were randomized to 24 weeks of either *mirtazapine* or placebo [108]. The results showed that mirtazapine produced a modest improvement in depressive symptoms, and was generally safe. The authors did not evaluate any effects on CHD outcomes. Since these early trials were published, other groups of scientists have tried different treatments and combinations of treatments with mixed results. The following two trials have relevance for this thesis:

CREATE-trial (Cardiac Randomization Evaluation of Antidepressant and Psychotherapy Efficacy, 2007), showed a modest effect on depressive symptoms with citalopram, but no additive effect of Interpersonal Psychotherapy (ITP) (n=294) [109].

COPES-trial (Coronary Psychosocial Evaluation Studies Randomized Control Trial, 2010), showed a modest improvement in depressive symptoms and a reduction in secondary cardiac events that was based on 3 (treatment) vs. 10 (care as usual) new events (n=157). Patients with persistent depressiveness were recruited three months after index events and received six months of problem solving therapy (PST) [110]. The study cohort was followed for 12 months, and the results were reversed with 11 events in the treatment arm vs. 3 in the control arm [111].

The overall state of the evidence for psychopharmacological treatment of depressive symptoms in CHD patients was evaluated in a 2011 Cochrane review, and the authors concluded that:

“Psychological interventions and pharmacological interventions with SSRIs may have a small yet clinically meaningful effect on depression outcomes in CAD patients. No beneficial effects on the reduction of mortality rates and cardiac events were found. Overall, however, the evidence is sparse due to the low number of high quality trials per outcome and the heterogeneity of examined populations and interventions” (p. 2)[112].

Here, it is noteworthy that the conception and design phases of most of the cited early trials took place during the era when the antidepressants were having their days of glory, and when the results were published, the effectiveness of these drugs had become subject for heated debate. It has been pointed out that many of these trials excluded the most severely depressed patients, which ironically might be the only group that would have had a significant beneficial effect from the treatment [113].

In an attempt to resuscitate some optimism in the field, Liu and Ziegelstein published an article in 2010 that made a case for more trials. The authors glanced back a couple of decades in time and reminded readers that the field of cardiology faced a very similar challenge with the first generations of lipid-lowering drugs. In 1990, the available evidence did not support that lipid-lowering drugs could reduce cardiovascular mortality, and there was concern about harmful side effects. This situation changed dramatically when the more effective drugs (*statins*) became available. This story, the authors argues, suggest that we might have to wait for better antidepressants before we can observe an effect on cardiovascular mortality [113]. Unfortunately, we have not seen any new magic bullets for the treatment of depressive symptoms during the last decades even though there are some promising new treatments under study (e.g., the anaesthetic *esketamine*) [114]. However, we do have other means to treat psychopathology than pharmacologically, although most of them are both more expensive and more demanding than swallowing a pill.

17. Other Psychological Risk Factors and Coronary Heart Disease

ANGER & HOSTILITY

When the Type-A behaviour had lost its status as a heart-toxic personality trait, some researcher scrutinized their data and found that it seemed to be the hostility part that was the toxic ingredient [115]. Hostility, being a basic negative orientation toward other people, is a complex phenomenon and the word denotes a broad domain with different cognitive, emotional and behavioural facets [116]. Although often used somewhat interchangeably with anger, hostility could be viewed as an attitude, while anger represents an emotional state [117]. Cynicism, on the other hand, refers to a general negative view of human beings in general, viewing other people as unworthy, deceitful and selfish. In a meta-analysis of 21 studies of healthy populations and 19 studies of CHD populations, all with CHD incidence as the outcome, Chida and Steptoe showed that anger and hostility as a group represented a significant risk factor. In the healthy sample the pooled increased risk was estimated to an HR of 1.19 (CI 1.05-1.35), and in CHD populations the increased risk was estimated to HR 1.24 (CI 1.08-1.42). The authors conclude that the result of the meta-analysis supports the use of psychological interventions in the treatment and prevention of CHD [117]. In *Study II* in this thesis, *cynicism* and *hostile affect* were measured with subscales from the Cook-Medley Hostility Scale, which was further psychometrically refined by Barefoot et al. in 1989 [116].

VITAL EXHAUSTION

During the same period when researchers started to pay attention to anger and hostility, Appels et al. observed that a considerable proportion of CHD patients reported high levels of fatigue before their acute coronary event. They decided to study the phenomenon of exhaustion in the CHD context and devised a self-report measurement for this purpose. Their new scale, the Maastricht Questionnaire (MQ), aimed to capture excessive fatigue, persistent feelings of demoralization and increased irritability and coined this triad of symptoms *vital exhaustion* [118].

A large body of evidence, collected during the 30 years that have passed since Appels et al. published their first article, has consistently found that vital exhaustion represents a substantial risk factor for CHD. In a recent and large prospective population based study of 8882 Danish study subjects, Schnor et al. showed that vital exhaustion, dichotomized as high or low, was one of the most important predictive risk factors for first time CHD, compared to traditional factors like blood pressure, tobacco smoking etcetera [119]. Recently, Cohen et al. summarized all prospective studies to date in 2017 and performed a meta-analysis of 17 studies [120]. They showed that vital exhaustion was significantly associated with increased risk of both CHD events (HR 1.53 CI 1.28-1.83) and all-cause mortality (HR 1.48 CI 1.28-1.72). In another meta-analysis of the same literature, Frestad and Prescott reported (unsurprisingly) almost identical results [121]. Interestingly, Biachi et al. commented on the Frestad and Prescott article in a letter to the editor [122]. The authors criticized the collected vital exhaustion literature, and indirectly the results of the meta-analysis, for neglecting the significant overlap between depressive symptoms and the measure of vital exhaustion. The symptoms measured in the vital exhaustion questionnaire, including a lack of energy, sleep difficulties, cognitive impairment, death wishes, feelings of hopelessness, loss of libido and persistently low mood is almost identical to diagnostic criteria for major depressive disorder (MDD). They further remark that only one of the studies included in the meta-analysis controlled for depressive symptoms, and with that adjustment vital exhaustion no longer predicted CHD. The study Biachi et al. cited was *Study II* in this thesis.

HOPELESSNESS

Hopelessness represents an orientation towards the future that is characterized by negative beliefs and, of course, a lack of hope. Depending on the time frame and pervasiveness of the phenomenon, hopelessness could be viewed as either a transient state or a more persistent trait [123]. One of the first prospective studies to investigate how hopelessness predicted CHD incidence and mortality was a 1996 study by Everson et al. [123]. They measured hopelessness with two items borrowed from an undefined “battery of psychosocial questionnaires,” and used the scores as a dichotomized variable (low vs. high hopelessness). High hopelessness scores were associated with significant higher risk of both CHD (HR 2.52 CI 1.52-4.17) and all-cause mortality (HR 2.26 CI 1.59-3.21), even after adjustment for depressive symptoms, measured with the Minnesota Multiphasic Personality Inventory (MMPI).

More recently, Pedersen et al. showed that hopelessness was associated with worse clinical outcome two years after PCI (HR 3.44 CI 1.65–7.19) [125]. Interestingly, Pedersen et al. presented hopelessness as a symptom of depression, and the measurement of both depressive symptoms in general and hopelessness in particular, was made with items from the MQ-questionnaire of Appels et al. *Study II* in this thesis include outcome data of hopelessness measured with the two items used in the Everson study.

ANXIETY

Anxiety is a common and complex psychological phenomenon that has attentional, cognitive and affective features that result in an experience of fear, uncertainty, and tension, which results in avoidance of perceived threats [126]. Anxiety can represent a transient state, or as a habitual disposition to experience fear and nervousness frequently. Often, an anxious disposition has been present since early childhood but traumatic experiences and chronic stress can trigger anxiety at any time in the life course [127]. Compared to e.g., hostility, vital exhaustion, and hopelessness, it is much easier to see how anxiety might be a highly preserved function that natural selection has shaped in humans to support survival. A simple example is the sense of dread many people feel when finding a poisonous snake in their kitchen, which would be a display of an adaptive and context congruent response. However, there are many instances when bouts of anxiety become dysfunctional rather than functional, and for many people, anxious experiences not only show up in an untimely and unnecessary manner but also reach hurricane levels of emotional storm (panic attacks) and often result in severe disability. Thus, similar bouts of fear and nervousness could be a perfectly normal and normative emotional reaction, or a disabling symptom of a psychiatric disorder, depending on context, and also, to some degree, who is judging the situation.

When evaluated according to present diagnostic criteria, pathological levels of anxiety seem to be very common. If anxiety disorders are treated as one group, they become the most prevalent psychiatric disorders, even outnumbering major depressive disorders. It has been estimated that one in nine people will have experienced an episode of an anxiety disorder during the past year [127]. Anxiety is twice as common among women, and the variation between different countries is large, e.g., 3 % in Italy and 30 % in Mexico [128]. The treatment of choice for anxiety disorder is psychotherapy, and CBT is often recommended based on the methods early arrival at the evidence for effectiveness. However, reviews have given similar credence for the effectiveness of psychodynamic therapy (PDT) [129] and Acceptance Commitment Therapy (ACT) [130].

According to a recent review article, anxiety disorders usually respond well to pharmacological interventions, and the most common treatment is with an SSRI or a selective serotonin and

noradrenaline re-uptake inhibitor (SNRI). A second line of treatment is the more controversial benzodiazepines [127].

According to the diagnostic nomenclature, anxiety is sub-categorized into generalized anxiety disorder (GAD), social anxiety disorder (SAD), panic disorder and specific phobias [56]. When taken into account as a potential risk factor for CHD, both symptoms of anxiety and anxiety disorders have been investigated, and a variety of different measurements have been used [131]. Recently, Emdin et al. summarized the literature on anxiety and CHD and conducted a meta-analysis that included 46 cohort studies [132]. The authors showed that anxiety was associated with a significant elevated risk of CHD; RR 1.41, CI 1.23-1.61, and cardiovascular mortality; RR 1.41, CI 1.13-1.76. Furthermore, they also found that phobic anxiety was related to higher CHD risk compared to other subtypes of anxiety. The GAD-7 scale was used in *Study III* as a secondary outcome measure.

A NOTE ON PSYCHOMETRICS – THE MEASUREMENT OF PSYCHOLOGICAL FACTORS

If researchers are to trust that they measure the phenomenon of interest with both accuracy and reliably, their instrument (in this case the questionnaire) will have to be critically evaluated in a *validation process*. Ideally, the instrument should be validated in the specific context the researchers intend to use it since the validity to some extent is context dependent [133]. It is also of vital importance that evidence for the validity of a certain instrument is collected from multiple sources [134].

The vast majority of studies of psychological risk factors and resources reviewed above, as well as in the next chapter, have used self-report instrument to measure the construct in question. Many self-report instruments include at least a few inverted items, which is questions that have words and meanings with the opposite valance or qualities. For example, the CES-D scale has 4 *positive* items, and the researcher have to flip the score on these items when coding the results. The purpose behind the inclusion of inverted items is to lower the risk that participants become bored and start to answer the questions in a sloppy and unengaged manner [135].

The question of inverted items and validity was the focus of *Study I* of this thesis, in which the validity of the two psychological resource scales Mastery and Self-esteem, and the depression scale CES-D was evaluated in the context of CHD risk. According to contemporary conceptualizations of *validity*, data from specific assessment instrument is more or less valid when the instrument is used for a specific purpose or in a particular context [133]. This aspect is essential to consider when using self-report instruments developed for measurements in psychological context in a cardiovascular context. This context- and purpose aspect of validity is one crucial reason for why *Study I* in this thesis is important. Furthermore, the validity of an instrument is generally strengthened if the evidence in support of its validity comes from multiple sources [133]. This ontological fact is one reason for our choice to use four different criterion measures, including both psychological and biological variables, in *Study I*.

18. Psychological Resources and Coronary Heart Disease

Almost 40 years after the initial interest for of Type-A behaviour and its toxicity, researchers started to pay attention to psychological resources in the context of CHD. During these four decades, most energies were spent on attempts to help people deal better with stress, and even positive functioning was studied as different ways people dealt with stress and situations perceived as threatening and distressing. The terminology and the research that followed reflected this fundamental outlook on human beings as utterly vulnerable, and more often than not, broken by modern life [41].

A pioneer in this regard that in many was half a century before his time, was the University of California Berkley psychologist Richard Lazarus (1922-2002). During a period when American psychology was dominated by behaviourism and psychopathology, Lazarus presented a model for coping with stressful situations that presented human beings as more active, creative and resourceful agents in their own lives [136]. In 1966, Lazarus published the book *Psychological stress and the coping process*, in which he emphasized the role of a rapid cognitive appraisal that shaped peoples emotional response to stressful situations. Furthermore, he described different styles or strategies people use for dealing with distress, including problem-focused and emotion-focused strategies [136].

In a 1987 review, Haaga was writing about contemporary and preliminary results and methodological questions that in many ways mirror the subsequent hunt for a depression treatment for CHD patients [137]. The review reports a rising trust in cognitive-behavioural interventions. It is also humbling to read about partially successful attempts to affect Type-A-traits with Beta-blockers and arguments about reciprocal relationships between physiological and psychological reactivity and arousal. Since we are going to introduce the practices of mindfulness meditation and yoga in subsequent chapters, it is interesting to note that various relaxation techniques and bio-feedback therapy were among the first to be evaluated in MI-patients with Type-A-behaviours. Haaga cites a trial from 1976, in which eight weeks of training in *Jacobsonian relaxation approach* (today known as progressive relaxation), failed to lower levels of anxiety in patients. The author speculates:

“Muscle relaxation training alone may not provide a sufficiently flexible repertoire for coping with stressful situations, including worry about time wasted on relaxation training itself” (p.559) [137].

In various schools of theoretical and clinical psychology, psychological resources that provided a buffer against the inevitable hardships of life had been on the radar screen since the 1960s, and researchers interested in character- and personality traits had tried their best to dissect human strengths and weaknesses for decades [138].

SELF-ESTEEM

Even though the subfields of personality- and social psychology were flooded with constructs like optimism and self-esteem, it took surprisingly long before they were investigated in the context of CHD. The construct of self-esteem, initially investigated by Rosenberg et al. during the 1960s, spurred a large number of studies of its vital importance for both mental health and for success in life. When thirty years of data collection and debate could be summarized in 1995, Rosenberg et al. proposed that self-esteem have two distinct dimensions; one that denoted a sense of self-worth in general, and a second more instrumental that was grounded in comparison with other people's competences [139]. Stamatakis et al. investigated self-esteem, measured with the Rosenberg scale,

in the Kuopio Ischemic Heart Disease Study, which was a longitudinal cohort of 2682 Finnish men and women, aged 42-60 [140]. Primary outcome was CHD mortality, and the data was derived from a national registry. The authors showed that there was a strong negative relationship between self-esteem and CHD mortality, with the lowest tertile of self-esteem having a two-fold risk (HR 2.0 CI 1.3-3.2). However, the association was attenuated when the researchers adjusted for behavioural risk factors, socioeconomic status and other psychological factors, including hopelessness, depression, cynical hostility, and sullenness. In fact, when they adjusted for hopelessness alone, there was no additional heightened risk with low self-esteem. The study of Stamatakis et al. provides intriguing results since it highlights an important question: Is it sound epidemiological practice to adjust for as many behavioural and psychosocial variables as possible, or could it be unwise to control for factors that might be the one mediating the observed relationship? The study is also of particular interest since the Rosenberg Self-esteem scale was used in two of the four studies in the present thesis. The scale and its anchors could be found in Appendix A.

MASTERY

In 2006, Surtees et al. published results from the EPIC-Norfolk study, which was a prospective cohort study of 20323 participants, aged 41 to 80 years, who were followed for an average six years [141]. Their analyses showed that participant's sense of mastery was associated with lower rates of mortality of cardiovascular disease, both when adjusting for age, sex and prevalent chronic diseases, and when also adjusting for smoking, social class, hostility, neuroticism, and extraversion. The longitudinal design and the outcome measure CHD mortality provides substantial evidence that a sense of mastery actually might protect against CHD, but mortality is a somewhat blunt assessment since a significant proportion of people with first time CHD survive their acute coronary event. The instrument that Surtees et al. used to measure participants sense of mastery was the Mastery scale, developed by Pearlin and Schooler in 1978 [142]. The context Mastery was embedded in was a broader conceptualization of the coping process people engages in when under stress.

"Psychological resources are the personality characteristics that people draw upon to help them withstand threats posed by events and objects in their environment. Mastery concerns the extent to which one regards one's life as under one's own control, instead of being fatalistically ruled."
(p. 5)[142].

In a later review article, Pearlin referred to empirical studies and argued that the construct of mastery represent a somewhat stable trait that is grounded in learned appraisals of one's coping capabilities in relation to the life circumstances one have to face [143]. The construct and measurement of mastery have a central place in this thesis since three out of four studies include mastery as an outcome measure. The scale and its anchor are shown in Appendix A.

OPTIMISM

In 2006, Giltay et al. reported data from the Zutphen Elderly study of 545, previously CHD-free, participants aged 64-84 years, who were followed for 15 years [144]. Participants were asked to respond to a 4-item questionnaire measuring dispositional optimism, every 5th year, and the researchers tracked who died and from what cause. The authors showed that the top tertile (third) of optimists had a 0.45 HR (CI 0.29-0.68) compared to the lowest tertile (the pessimists), and this association showed a graded dose-response pattern. The association also remained when adjustments were made for depressive symptoms.

EMOTIONAL VITALITY

In 2007, the first prospective study of a psychological resource and its relationship to CHD incidence was published. Kubzansky and Thurston reported results from a large prospective study of 6025, previously CHD-free men and women, aged 25-74 years, who were followed for a mean 15 years [145]. The construct *emotional vitality* was measured with three subscales (vitality, positive well-being, and emotional self-control) from the 6-subscale General Well-being Schedule. The authors showed that the highest tertile of emotional vitality, compared to the lowest, showed a marked decrease in CHD risk (RR 0.81 CI 0.69-0.94) for both men and women, also after adjustment for health behaviours and depressive symptoms.

LIFE ENJOYMENT

In 2009, a second prospective cohort study reported data of a psychological resource and CHD incidence. Shirai et al. reported data from a large Japanese cohort study of 88175 men and women, aged 40-69 years [146]. Participants were followed for a median of 12 years, and the authors measured *perceived life enjoyment* with a single item (are you enjoying your life?) with three alternative answers (low, medium and high). The authors showed that perceived life enjoyment was negatively associated with CHD incidence, HR 1.22 CI 1.01-1.47, but only for men but not for women. These results were the same when adjustment for perceived stress and Type-A-traits were made.

POSITIVE AFFECT

In 2008, Nabi et al. reported data from the prospective British Whitehall II study. A cohort of 10 308 civil servants, aged 35-55 years, were followed for 12 years [147]. The authors investigated the independent association of *positive*- and *negative affect* on incidence in CHD. Affect was measured with the 10-item Bradburn Affect Balance Scale. The authors found no significant relationship between positive affect and CHD risk (HR 1.01, CI 0.82-1.24) and only a weak association between negative affect and CHD risk (HR 1.32 CI 1.09-1.60). In 2010, Davidson et al. published the results from the Canadian Nova Scotia Health Survey [148]. The authors studied *positive affect*, measured with a semi-experimental interview setting called the Expanded Structured interview. The 12 min interview paradigm was initially designed to study Type-A-responses to stress, and in this study, the researchers added how they expressed positive emotions, either verbally or in behaviour (e.g., smiling), or tone of voice. The authors found that positive affect was negatively associated with CHD risk (HR 0.78 CI 0.63-0.96) and this association was not attenuated by adjustment for depressive symptoms (measured with CES-D), hostility or anxiety.

SENSE OF COHERENCE

The medical sociologist Aaron Antonovsky (1923-1994) was a pioneer when it comes to resourcefulness and health, and he studied concepts like *meaning* decades before anyone called this perspective “*positive*.” Antonovsky, who had performed sociological research at Yale University and immigrated to Israel in 1960, used the term *salutogenesis* to describe the web of psychosocial factors that contributes to preserved health in the face of stress and traumatic experiences [149]. Antonovsky constructed a self-report measure to capture salutogenic psychological factors, which he called *Sense of Coherence* (SOC). SOC include three distinct dimensions: *meaningfulness*, *comprehensibility*, and *manageability*. Studies of SOC and CHD have yielded conflicting evidence. In the prospective study of Surtees et al. cited above, high SOC was associated with decreased mortality and cancer mortality, but not cardiovascular mortality [141]. Poppius et al. compared SOC to traditional cardiovascular risk factors, in a study of 4405 middle-aged Finnish men with

different occupations, in a prospective 8-year follow-up study [140]. They showed that SOC had a protective effect among white-collar, but not blue-collar workers. In a previous publication on the same cohort, the researchers reported the same pattern for CHD incidence with striking differences between high and low SOC among white-collar workers, but a paradoxical lower incidence among blue-collar workers with low SOC [151]. A 13-item version of the SOC-scale was used in *Study II*.

SENSE OF PURPOSE

A related construct is a *sense of purpose*. This broad psychological phenomenon has also been linked to CVD (CHD and stroke). Koizumi et al. Showed that sense of purpose, measured in 2959 subjects (40-74 years old), was associated with a significant decrease in 13 year CVD risk (HR 0.28 CI 0.10-0.84, for those with strong, compared to those with weak sense of purpose [152].

19. Positive Psychology

Just as the wave of antidepressant trials was related to strong trends in psychiatry, the above-cited studies reflect a similar trend in personality- and clinical psychology. When the 20th century was coming to an end, critical voices in psychology were raised against the limiting perspective dominating clinical psychology, with its almost exclusive emphasis on psychopathology. Echoing the more whole-person oriented perspective of William James, and the human potential perspective of the humanistic movement, the novel field of *positive psychology*, started to take up space in psychology [153]. Proponents like Martin Seligman, who studied happiness, and Mihaly Csikszentmihalyi, who studied peak experience and peak performance and associated states of *flow*, were founding fathers of the growing branch of positive psychology. By studying positive traits and states, strengths and virtues, they argued, psychology could be transformed into a positive and genuinely preventive science of human potential [40].

Positive psychology was not so much a movement with radical new ideas, theories, and hypothesis, but more a process of resuscitation of old ideas, packed into a more serious scientific language and backed up with data. According to Seligman, the humanistic movement of Maslow and Rogers made a significant impact on the culture at large and inspired a whole generation of therapists, but it failed to gather empirical support and thus to take up permanent space in academic psychology. Instead, Seligman speculated, the humanistic movement became mixed up with the over-enthusiastic self-help-business. [153].

When Dubois et al. reviewed the literature available in 2015 on the relationship between positive psychological constructs and health outcomes in patients with CHD, they found 11 studies where effects on rehospitalisation or mortality were reported. Most but not all studies found protective effects and the authors concluded that additional work is needed to identify which constructs are most important to cardiac health and whether interventions can cultivate positive attributes [154]. This is precisely the gap in knowledge we address and aim to begin to fill out with *Study II* and *III* in this thesis.

20. The Bio-Psycho-Social Model and Coronary Heart Disease

The intersection of psychology and biology is complex beyond measure, and many of the links we will cover are still incompletely understood. Researchers usually handle this complexity by sticking to the angle that is most familiar and reduces complex webs of interacting factors into a few distinct phenomena [155]. Before we start to dissect the web of links that connect our minds to our hearts, we will briefly return to a historical period when psychological factors were out in the cold.

During the end of the 1970s, the psychiatrist George L. Engel (1913-1999) launched his efforts to convince the medical establishment to take psychological and social factors just as serious as biochemical and physiological. Engel, in many ways reflecting the Gestalt movements' criticism of behaviourism, argued that the prevailing model of disease was deeply flawed and that the whole field of medicine was in crisis. In his 1977 article in the journal *Science*, Engels diagnosis of the state of affairs was brutal [156]. The crisis, according to Engel, came from a narrow and reductionistic focus on finding biochemical explanations to all medical and psychiatric problems. Grounded in this critique, Engel proposed an alternative *Bio-Psycho-Social model* (BPS), in which the physician, or scientist, would take all these factors into account.

The partial success of Engels BPS model is evident from the fact that researchers, educators, and clinicians still argue and publish lengthy articles about it [157]. However, the model has been criticized for not being a model of practical value (e.g., guiding clinicians and researchers in solving problems) [158]. Some critical voices have questioned the validity of the original divide between the biomedical model and the bio-psycho-social model and pointed out that biomedicine always has been too complex for being viewed as a single model, and that Engels critique make use of straw man argumentation [159].

What was missing in 1977, but is beginning to emerge today, was both a scientific explanation of the mechanisms linking the psychological- social- biological domains, and a willingness to address the remaining and tough questions about subjective experience. Even though considerable progress has been made in the scientific study of psychological risk factors and resources in the context of CHD, there are still significant gaps in our understanding of the mechanisms that connect the three levels to each other. Furthermore, there is an even more significant gap between what we know and what kind of help we offer to patients in need.

Study I and *II* in this thesis, directly address the rather straightforward question of the impact of psychological variables on CHD risk, while *Study III* and *IV* address the more complex question of finding a solution for a suitable and effective way to address the suffering of selected CHD patients. All four studies included in this thesis are mainly focused on the *bio-psycho* part of the BPS-model, and as a result of the aims and research questions addressed, they do not study the *social* part. However, the results from especially *Study II*, which investigate the impact of psychological risk factors and resources, could add sharper hypotheses to the study of which mechanisms mediate the intricate relationships between social and biological variables.

21. The Psychobiology of Stress

A theme that returns again and again in this introduction is *stress*. The field of psychosomatic medicine, with Cannon and Seyle as pioneers, was grounded in the discovery of the physiological stress response, and when the cardiovascular field became interested in psychosocial factors, it was stress and its downstream attributes of impatience, competitiveness, and exhaustion that became the initial focus. From this, it comes as a natural consequence that much of what we know about the biological mechanisms between mind and heart are related to the biology of stress.

The physiological term for the organisms fight against the universal tendency of increasing entropy, coined by Walter Cannon, was *homeostasis*. Homeostasis refers to the steady state in the body's *internal milieu* that various physiological systems collaborated to maintain at all costs since the proper function of the organism is dependent on this steady state [160]. For our purpose here, it could be enough to summarize the broad structure of this interconnected system.

We are equipped with senses that provide detailed information about both the outer and inner environment, and fish-like parts of the nervous system that regulates physiological processes and basic arousal and wakefulness processes. On top of these structures, and integrated to the *fish-brain*, lays a reptilian brain that complements the raw perceptual process with emotional tones and cognitively derived understandings of the *meaning* of this information. This structure, which is also known as *the limbic system*, contains two fear-processing nuclei of the *amygdalae*, and structures that are related to attention and memory (*the hippocampus*). On top of these we have higher evolved structures, e.g., the *cortex* of the *frontal lobes*, that regulates more complex emotional- and cognitive functions. These responses could be balanced and appropriate in relation to the context and environment (e.g., when we respond wisely), or distort the process of information flow in such a way that the behavioural response either shoot over the target (e.g., anxiety), or fail to recognize the proper meaning of events (e.g., depression) [155].

- + Parts of the sapiens brain, which are associated with fear; especially the *amygdala*, will come fully on-line and signal an alarm to other parts of the brain (including the *insula*, which recognizes the emotional tone of the limbic activity) and other branches of the nervous system:
- + Two branches of the *autonomous nervous system* (ANS), relay information from the brain to peripheral organs and back again. They are called the *sympathetic branch* (the gas pedal of the stress response) and the *parasympathetic branch* (the brake pedal). During a stress response sympathetic activity increase and parasympathetic activity decrease within seconds.
- + Peripheral organs, with innervation from ANS, respond to the changes in specific ways (e.g., according to the pattern of connectedness and the presence of specific receptors).
 - + *The heart* speeds up and pumps with more powerful strokes, to deliver more oxygenated blood to hard-working muscles in the body, as well as till the brain that tries to coordinate the whole circus.
 - + *Great blood vessels* throughout the body stiffen to raise the blood pressure, to further support fast and effective blood flow. Other blood vessels relax to further facilitate effective delivery of oxygen and fuel.
 - + *The GI-tract* and *the kidneys* decrease their blood flow as means to direct it to the most acutely important places in the body (you pause the metabolism of your lunch when you risk becoming someone else's lunch).
 - + *The liver* and large *skeletal muscles* release their stored glucose (glycogen), and thus providing working muscles and the brain with fuel.

Increased activity in the *sympathetic branch* of the ANS also stimulates the medulla of the *adrenal gland* to release the hormones *adrenaline* and *noradrenaline*. These so-called *stress hormones* reach every corner of the body and have similar, and amplifying, actions as the ANS.

When an organism registered stimuli that are interpreted as a threat many things are subsequently happening in the body and mind. Alarm signals from the amygdalae, and other limbic structures, signals to the *hypothalamus*, which is an important hub in the CNS, connecting parts of the brain concerned with the outer world with parts engaged in regulating the internal milieu. During the stress response, the hypothalamus releases *corticotropin-releasing hormone* (CRH), which travels through a small vessel to the *anterior pituitary*, which is a hormone-secreting gland inside the brain. The anterior pituitary releases *adrenocorticotrophic hormone* (ACTH) into the bloodstream, and within minutes, the cortex of the adrenal glands gets this signal and responds by flooding the blood with the hormone *cortisol* [155].

- + *Cortisol* is a steroid hormone that diffuses into various cell types of the body, binds to intracellular receptors, and travel to the DNA in the nucleus of the cell and change gene expression. The effects of cortisol in various tissues of the body are complex and the subject of much debate. For our discussion here it is most important to recognise the following broad features:
- + In the short time frame, cortisol tends to potentiate the actions of the ANS and the catecholamines (adrenaline and noradrenaline), and also feed-back at the amygdala, creating a positive feedback loop that increases the excitability in the CNS.
- + In the short time frame, cortisol also tends to stimulate the immune system (e.g., through the recruitment of white blood cells into the bloodstream).
- + In the longer time frame, sustained high circulating levels of cortisol are known to decrease many facets of the immune system, and disrupt its ability to regulate inflammatory processes, and respond adequately to acute or chronic infections.

Unfortunately, many of the functional adaptation to acute stress outlined above also happen to be potential and potent mechanisms for subsequent heightened risk of coronary artery disease. The psychobiological process of *stress* has been re-conceptualized as *allostatic load*, which mean that the cascades of cause and effect that begins with primary stress mediators, such as catecholamines and cortisol and leading to primary effects and then to secondary and tertiary biological and psychological outcomes. The term *allostasis*, which denotes the maintenance of homeostasis through change, was first introduced by Sterling and Eyer [161], and have been further developed by Bruce McEwen and his colleagues.

Repeated activation of the stress-response system could over time result in dysregulation. First, the response could be prolonged due to delayed shutdown (e.g., during chronic stress). Second, there could be a lack of adaptation to stress-evoking stimuli, which leads to cumulative wear and tear from repeated stress responses. Third, stress responses could come so frequently that recovery is not allowed. Any of these variants of stress-load could lead to dysregulation in either the form of an inability to respond when necessary (under-responsiveness) or to a sensitized system that becomes hyper-responsive to new stimuli [162].

CHD patients have often increased *platelet activity*, and this increase may be even more pronounced in depressed CHD patients [163]. This mechanism has relevance for both acute and chronic stress. *Endothelial dysfunction* is a feature of the atherosclerotic process, and there are studies linking this mechanism to cynicism and hostility, as well as experimental studies of laboratory stress [164]. *Overactivity of sympathetic activity* in the ANS, and under activity of the parasympathetic branch, has been found in both CHD patients and among depressed individuals in the general population. These

dysfunctional adaptations could result in high blood pressure, increased demand on the myocytes, and contribute to arrhythmias [163]. Although there is some controversy in the literature, it has been shown that chronic stimulation of the HPA-axis can lead to hypercortisolemia blunted responsiveness and diminished feedback-control of the hormonal axis [47].

The combined effect of dysregulation of ANS and the HPA-axis (perhaps worsened by lower levels of GH and sex hormones, can lead to insulin resistance and high levels of blood lipids. These alterations could contribute to the development of type-II diabetes mellitus, which is a potent risk factor for CHD [47]. Atherosclerosis, as we have seen, is a pathological process with increased and *dysregulated inflammatory activity* in the arteries. In addition, CHD patients with high levels of circulating markers of inflammation, e.g., cytokines and CRP, have a greater risk of new coronary events [163]. Garvin et al. showed that psychological risk factors and resources, are independently associated with a circulation biomarker for vulnerable atherosclerotic plaque, called Metallo-Matrix-Proteinase-9 (MMP-9) [165].

Additional support for the mechanism of stress, that received attention in the public media in 2017, was a study by Tawakol et al. They studied 293 patients that went through a PET-scan (a CT procedure with a radioisotope). The authors showed that activity in amygdala was related to inflammatory activity in the large arteries and incidence in CHD. In a small subgroup of patients, they also found that perceived stress was associated with amygdala activity, arterial inflammation, and CRP [166].

The four studies included in this thesis did not measure any biological aspect of the stress response, nor did they investigate any acute reactions to stressful experiences. Instead, *Study I* and *II* are dealing with psychological resources that might be important buffers against the negative effects of repeated or sustained activation of the stress response, and alterations in this intricate system might thus be one of the direct mechanisms mediating the relationship between the psychological variables and CHD. As we will see in chapters 30-32, the psychobiological theory of stress will also represent one of the mechanisms that could explain why the mindfulness-based intervention, investigated in *Study III* and *IV*, could have salutary effects on CHD.

THE PSYCHOBIOLOGY OF RESILIENCE

The human organism has evolved a complex central nervous system, and its interaction with the environment allows for the emergence of consciousness and various interconnected psychological processes [167]. Our minds also use earlier experiences, stored as both explicit and implicit memories, as well as values and goals, to refine or distort the whole chain of events, from stimulus to behaviour [155]. Thus we have filters of early experience and expectations that colour perception and appraisal (with simulations and predictions) and we have attitudes and emotional processing styles that influence behavioural tendencies and resulting responses [168].

When a stimulus from the environment, or from within, is perceived as threatening, it immediately engages psychological processes of *attention regulation* and *awareness*, so that it recruits cognitive and emotional resources to be concentrated to the perceived threat. Studies have shown that negative emotions, like fear, anxiety and low mood, tend to narrow the scope of attention, while positive emotions like joy, well-being, and gratitude tend to broaden the scope of attention [169]. When a situation is perceived as a threat, a human being experience internal reactions and alarms signals as *emotions* like fear, anxiety or even panic. How the interlinked psychobiological chains of events translate into a subjective experience of an emotion, is still much debated and a hot topic in psychology [170]. Some argue that activation of nuclei deep down in the reptilian brain results in a few primary emotions, which gets mixed with cognitive interpretations to form a broad range of

secondary emotional experiences [171]. Other researchers emphasize that basic emotions depend on the physical expression, especially facial expressions, that feedback an emotional tone to the experience in question [172]. Others still, oppose the biological paradigms and argue that emotions are irreducible psychological phenomena, constructed at the psychological level, and thus not distinct biological in nature [170].

When a threatening situation has been triggered, the human mind could either amplify the initial response with forecasts of catastrophe or dampen the initial response with learned perceptions of coping abilities. *Emotional regulation* is a very complex and incompletely understood process. Here it most of all important to note that the human psyche can either handle an emotional experience constructively and successfully – leading to adaptive and healthy behaviour, or destructively – leading to maladaptive and unhealthy behaviours [173].

Perspective regulation is not a common term in psychology, but it is used here as an umbrella term for cognitive facets of the psyche's way to handle a stressful situation. As such it includes cognitive processes of both fast and slow appraisal of a situation, the following interpretation of the meaning of the situation, and the executive decision making of how to act. As we have learned from the cognitive theory of depression, some people have a high degree of bias, stemming from a cognitive filter that results in misapprehensions of various situations and contexts [38]. From a behaviouristic perspective, people's appraisals are very much influenced by prior learning and constructive or destructive perspective taking could influence the development of psychopathology [174].

The divide between emotional and perspective regulation is artificial, and in reality, they are interconnected and mutually influential, and they are also linked to attention and awareness processes in a bidirectional fashion [167]. Emotions can narrow attention and evoke both functional and dysfunctional cognitive schemata that result in accurate and measured or inaccurate and disproportional appraisals of a situation. At the same time, the regulated direction of attention can be applied to regulate emotional reactions successfully and to foster a sound perspective by delaying premature and instinctual conclusions about the nature of a distressful situation. Lastly, the different cognitive processes of perspective regulation could influence the magnitude or the duration of an emotional reaction and thus foster a more open attentional stance. This interconnected process has been called *self-regulation*, and this term describes a goal-directed behaviour that stems from constructive regulation of attention, emotions, thoughts and resulting behaviour through the deliberate or automatic use of specific skills or mechanisms [175].

According to contemporary conceptualisations coping and resilience, successful or dysfunctional self-regulation, interact with behaviour in ways that becomes mutually reinforcing [176]. Thus, frequent and intense negative emotions lead to narrow attention, a negativity bias in perspective regulation and in behaviours that aim at avoiding further negative stimuli, which paradoxically increase the sensitivity to negative stimuli, and we have a downward spiral with the development of psychopathology [173]. Conversely, frequent and intense positive emotions lead to a broadening and opening up of attention, curious and accurate perspective regulation, and results in behaviours that are dealing constructively with distress, and most of all concerned with opportunities rather than threats. This process results in an upward spiral of health and well-being [173].

Some researchers, citing recent evidence from primate- and fMRI studies, are proposing that one unified large-scale brain system is responsible for supporting allostasis, including immune function, and psychological functions, such as memory and executive functions, simultaneously [167]. From this perspective, psychopathology (e.g., depression) would reflect an inability to support allostasis and a failure to maintain a well-calibrated level of metabolism and represent a kind of emotional

“locked-in-syndrome” [177].

When self-regulation skills fail to develop properly, then even neutral and unharmful situations, including mental simulations like rumination and worry, evoke stress-responses. If there is also a learned fear of negative emotions or thoughts, we might have a cascade of feed-forward that resembles the hypersensitivity reaction seen when the immune system reacts to unharmful stimuli with allergy [178]. Conversely, well-developed self-regulatory skills could result in the development of a wide window of tolerance for various and intense emotions and bodily sensations. Combined with skilful perspective taking, this would lead to a growing capacity to handle the complex, stressful and even threatening situation with focused attention and a high level of tolerance for emotions, and result in adaptive coping behaviours and a limited or short-lived activation of the stress response.

If we would want to find a common language for the complex and interconnected psychobiology processes described in this introduction, without an artificial divide between *psychological* and *biological*, then the concepts of *tolerance* and *intolerance*, could serve us well. If we also want to include principles and processes from the Buddhist view of how a sound relationship to self and world contribute to the sustainability of psychological health we might need a broader framework [179]. We will return to this in chapter 26.

PART III

MINDFULNESS & CORONARY HEART DISEASE

22. Psychological Interventions in Coronary Heart Disease

In the diverse and disparate field of clinical psychology, the cognitive behavioural perspective, and its new manual-based therapeutic tools, took up increasingly more space. With influences from behaviouristic theories of learning and shaping of behaviours, and from cognitive theories of information processing and the importance of thoughts, the new *CBT-movement* was also catalysing its popularity by early adoption of the medical model of randomized clinical trials [180]. When reviewing the literature, it becomes apparent that this trend was spreading to the field of behavioural cardiology during the 1990s. To say that we have seen an explosion of RCTs with psychological treatment for distressed CHD patients would be an exaggeration. A recent and extensive review of published RCTs found 35 trials to include in their meta-analysis, while another 66 trials were excluded for various methodological reasons [181]. The following 12 trials of CHD patients are particularly relevant for the discussion in this thesis and have also been judged to have robust methodological qualifications:

INDIVIDUAL THERAPY

McLaughlin et al. (2005) showed that a 6-session problem focused therapy via telephone (vs. usual care) was moderately effective in reducing symptoms of depression and anxiety in patients that were screened and diagnosed with depression before enrolment (n= 100) [182].

Lie et al. (2007) evaluated the effects of a two-time home visit from a cardiac nurse (vs. usual care (n=185)). They found no differences between the two groups scores of anxiety and depressive symptoms. However, when they selected those with high symptoms at baseline (n=65) they found statistically significant benefits in the intervention group [183].

Freedland et al. (2009) compared two different 12-week psychological interventions (individual CBT vs. a supportive group setting) with usual care and showed that CBT had superior and more durable effects on a number of psychological outcomes, including depressive symptoms, anxiety hopelessness and stress (n=153) [184].

Davidson et al. (2010) demonstrated that a stepped-care intervention (vs. usual care) for depressiveness resulted in decreased symptoms and promising improvement in the risk of major cardiac events (n=237). The stepped-care intervention allowed patients, randomized into intervention-arm, to choose between problem-focused therapy and pharmacological treatment, and the treatment was intensified if the patients had not improved at regular 8-week evaluations [185].

Rakowska et al. (2015) investigated effects of brief problem-focused psychotherapy compared to usual care among patients with increased symptoms of stress at baseline. The intervention group showed reductions in perceived stress and at 1- and 2.5-year follow-up, patients had a lower risk of non-fatal and fatal re-infarction, respectively (n=81)[186].

GROUP-BASED THERAPY

Saab et al. (2009) published a post-hoc analysis of data from the ENRICHED-trial, cited above, that compared patients who received individual CBT-therapy with those who got both individual and group therapy (all patients were also taking SSRI). The latter group had a lower risk of subsequent cardiac events (HR 0.67, CI 0.49-0.97) (n=1137) [187].

Neves et al. (2009) compared cardiac rehabilitation, with additional 12 weeks of relaxation therapy, with ordinary cardiac rehabilitation. The former group improved significantly more on patient-reported perceived stress as well as measures of heart rate and blood pressure (n=81) [188].

Gulliksson et al. (2011) studied the effects of a 20 session, 1-year, group CBT-intervention focusing on stress-management, compared to usual care. They showed that the CBT-arm of the trial had a significantly lower risk of recurrent acute myocardial infarction (HR 0.59, CI 0.42-0.83) during a follow-up period of 8 years (n=362) [189]. A follow-up analysis of psychological mediators of the effect on recurrent MI and mortality showed that anxiety had a small mediating role, while perceived stress, vital-exhaustion and depression did not [190].

Schneider et al. (2012) investigated the effects of transcendental meditation (TM) (vs. health education) and showed that the meditation-intervention was associated with a significant reduction in subsequent myocardial infarction, stroke, and mortality. The also showed that lowered blood pressure and reduced perceived stress partially explained the risk reduction (n=201) [191].

Roncella et al. (2013) studied the effects of a humanistic/existential form of psychotherapy (*ontopsychological*) delivered both individually and in a group setting (vs. usual care). The treatment arm of the trial showed a reduced risk of subsequent cardiovascular events and had lower rates of re-hospitalization and improved depressive symptoms (n=94) [192].

Turner et al. (2013) reported findings from a trial in which six sessions of group CBT were compared with a brief single-session control intervention. They found neither any differences in remission in major depressive disorder nor any improvements in depressive symptoms between the two groups [193].

Blumenthal et al. (2016) showed that a group-based stress management program, based on CBT-principles, as addition to cardiac rehabilitation (vs. only cardiac rehabilitation) was associated with lower rates of subsequent clinical events (HR 0.49, CI 0.25-0.95) (n=151) [194].

Thus the current state of knowledge shows a dozen of different interventions has shown small to moderate improvements in psychological outcomes, and somewhat mixed results on cardiovascular outcomes and mortality. Richards et al. conclude that there is still considerable uncertainty surrounding the effects on hard endpoints and many studies have been associated with difficulties to recruit the patients most in need of interventions [181,113]. This relative lack of treatments with established effects, and proven suitability in the context of cardiac rehabilitation represents the rationale for the launching of a feasibility trial of a mindfulness-based stress reduction intervention.

23. A Brief History of Mindfulness in Medicine

At roughly the same time period as behavioural cardiologists were investigating various ways to help people cope with Type-A-behaviours, and getting them to become more socially connected, a less Americanized influence was starting to make an impact on the dynamic field of psychosomatic medicine; namely a resurrected interest for eastern philosophies, which now became increasingly brought into the medical context. The view that eastern philosophies have valuable insights to offer thinkers in the West was of course not a new phenomenon. Both Thoreau and Emerson had spiced their ideals of self-reliance and romanticism with ideas from the Hindu classic Bhagavad-Gita. The novelty with this interest for eastern wisdom traditions was that researchers began to study the effects of religious practices, such as yoga and meditation, in psychology and physiology labs at major Universities in both the United States and in Europe. A key example was the Harvard cardiologist Herbert Benson, who teamed up with proponents of a type of mantra-based meditation called transcendental meditation (TM) [41].

Initially, very reluctant to draw premature conclusions, Benson eventually gathered enough data to become convinced that both TM and other meditation techniques had the power to turn off the stress response. Benson studied physiological alterations produced during meditation and showed that what happened was not just a reduction of stress levels back to normal, but essentially a complete reversal of the flight-and-flight-reaction. Curiously Benson discovered this reversal of the physiological reaction to stress in the same laboratory at Harvard where Walter Cannon had discovered the fight-and-flight reaction half a century earlier, and he coined the phenomenon *the relaxation response* (which also was the name of his 1975 bestselling book) [41].

Four years after Benson published *The Relaxation Response*, a former doctorate student in molecular biologist and lecturer in anatomy at University of Massachusetts School of Medicine, named Jon Kabat-Zinn, started to gather patients with various chronic conditions and teaching them Buddhist practices of mindfulness meditation and gentle yoga poses. Kabat-Zinn had been involved in the study and teaching of insight meditation since he was a graduate student at MIT [195]. Eventually, the meditation and yoga intervention was developed into a 10-week long course, which was called *Stress-reduction and Relaxation Training* [196]. Kabat-Zinn and his colleagues streamlined the course into eight weeks and changed the name to *Mindfulness-Based Stress Reduction*, or MBSR for short. In 1985, Kabat-Zinn and a group of colleagues published a study on 90 patients with chronic pain who had participated in the 10-week Stress and Relaxation Training programme. Their results showed that participants improved significantly in present moment pain, negative body image, and they used less medication and had better self-esteem and activity level [196]. During the 1990s Kabat-Zinn published a best selling book called *Full Catastrophe Living*, which contributed to the spread of MBSR over the whole American continent and also to Europe and Asia, where pioneers visited the University of Massachusetts and brought the methods back home [195].

24. Mindfulness-Based Stress Reduction

Participants who sign up for the 8-week MBSR-course are expected to attend group practice sessions once a week, which consists of guided meditation- and yoga sessions as well as didactic teachings and group dialogue for 2.5 hours. The recommended group size is between 25 and 30 participants. In between group meetings participants are instructed to practice for around 40 minutes with CDs of guided meditation- and yoga lessons, and complete reflection exercises which are discussed at the following meeting. During week six, the participants are invited to a whole-day silent mini-retreat to deepening budding mindfulness skills. The structure and content of the MBSR

course are specified in an official manual [196], and adding new content is not recommended if the course is to be called MBSR. However, there is also a thread of spaciousness in the curriculum for room to work with what is brought up in any particular group [198]. A more detailed description of the content of MBSR could be found in Appendix C.

A group of researchers, who visited Kabat-Zinn and his patients during the second half of the 1990s, was the depression researchers and clinicians Mark Williams, John Teasdale, and Zindel Segal. Curious about if mindfulness could provide a solution for patients with major depressive disorder, they trained themselves in MBSR and created a modified version adapted to severely depressed participants. The result was a light-version of MBSR, with shorter practices and group meetings, and spiced with a few CBT-techniques. The course was named *Mindfulness-Based Cognitive Therapy* and in 2002 Teasdale et al. published a trial of 145 patients randomized to either treatment as usual or the addition of MBCT. Their results were impressive, at least among the most seriously diseased patients. For patients with 2 or fewer episodes of MDD, MBCT did not prevent relapse into depression, but for those with 3 or more episodes, MBCT in adequate dose almost halved the risk of relapse [199].

The field of clinical psychology had been made ready for embracing the philosophies and practices of mindfulness by pioneering work during the 1980s and 90s. The psychologist Marsha Linehan and colleagues developed a group-based psychotherapy for borderline personality disorder (BPD), called *Dialectic Behavioural Therapy* (DBT), which was based on CBT-principles combined with various emotional-regulation trainings, including mindfulness practice [200]. Initially designed for chronically suicidal patients, DBT evolved into a successful treatment for BPD, and has subsequently been found to be effective for many other psychiatric disorders. The behaviourally oriented psychologist Stephen Hayes, and his colleges, did not started out with a particular clinical problem, but took a stance in philosophical and empirical work on human behaviour and human suffering (a theory grounded in functional contextualism called *Relational Frame Theory*, or RFT). They developed a psychotherapeutic approach called *Acceptance and Commitment Therapy* (ACT) [173]. When a critical mass of clinicians and scientists became interested in DBT, ACT, MBCT and MBSR, they were grouped together under the umbrella term *third wave of psychotherapy* (the first being early behavioural therapy, the second being CBT) [174]. When scrutinized or reviewed as a group of treatment, these various *mindfulness-based interventions* are often referred to as MBIs.

Recently Crane et al. have explicitly outlined what constitutes the core of MBIs that should not be compromised in adaptations [201]: 1) Being informed by theories and practices from contemplative traditions, science, and medicine, psychology and education. 2) Is underpinned by a model of human experience, which addresses the causes of human distress and the pathways to relieving it. 3) Cultivates a new relationship with experience characterized by present moment focus, decentring and an approach orientation. 4) Supports the development of greater attentional, emotional and behavioural self-regulation, as well as positive qualities such as compassion, wisdom, and equanimity. 5) Is based on sustained and intense training in mindfulness as an experimental inquiry-based learning process, and based on exercises to develop insight and understanding. They also outline that teachers should: 1) Have the right competencies to effectively deliver guidance and content in the MBI. 2) Have the capacity to embody the qualities and attitudes of mindfulness within the process of teaching. 3) Have engaged in appropriate training and commits to on-going good practice. 4) Is part of a participatory learning process with their students, clients, and patients [201].

25. A Brief Introduction to Buddhist Psychology

Siddhartha Gautama lived sometime around 400 years B.C. in northern India [202]. His mother died shortly after his birth and growing up in the protected environment of a luxury court, he was subsequently shocked and deeply troubled by his encounter with poor, sick and dead people [203]. The Buddha became so consumed by hopelessness and despair over the pervasiveness of suffering in the world, that he left his wife and young child for a life as a wandering yogi and ascetic. Even though he was said to have been an extraordinary talented yogi, and pushed himself almost to the brink of death as an ascetic, the Buddha did not find inner peace in any of these methods of self-improvement. It was not until he gave up his frantic search of enlightenment, and sat under the Bodhi tree in Bodhgaya, and remembered the ease of dropping into and aligning with the natural rhythm of life, that he finally became the awakened one, which is the meaning of the word *Buddha*. He then spent the rest of his life teaching people from near to far what he had realized was the solution to the human predicament, which was *the four noble truths* and their applications in *the eight-fold path* [204].

At its core, the Buddhist psychology is built around the notion that the human mind ordinarily perceives things and events as attractive and pleasant, which creates *craving* and attachment, or as repulsive and unpleasant, which creates *aversion* (another kind of attachment). Both of these *perceptual filters*, or *modes of appraisal*, tend to distort the view of reality, and this, in turn, leads to misapprehension and impairment of the ability to perceive reality correctly. This impairment in discernment does not only lead people to think, speak and act with biased views but also prevent them from realising some fundamental truths about existence; e.g., the *impermanence* of everything and the ultimate lack of *independent existence of the self*, things, and events. From this view follows that it is not useful to label emotions as *positive* (e.g., joy) or *negative* (e.g., anxiety) as in western psychology, but rather as *constructive* or *destructive*, depending on whether they lead to more clarity of perception, or to more distortions [205]. A second core principle of Buddhist psychology is that the majority of suffering in human beings is derived from an instinctual *identification process*. The Buddha recognized that this identification, which he called a *clinging to a sense of I, me or mine*, lies at the heart of the creation of attachment and aversion, and thus represents the main source of psychological suffering.

The solution, presented by The Buddha, was to systematically train the mind in ways that address the core problems of attachment and aversion, from two directions; firstly to enhance clarity of perception by the training of wakefulness and attention skills, and; secondly, by reducing the frequency and influence of destructive emotions through the cultivation of *equanimity* (emotional regulation skills). When practiced over time, these skills enhance the ability to relate to the experience of life with more clarity, insight, acceptance, and wisdom. The Buddhist practices also aim to improve “*positive*” qualities, since the cultivation of awareness and equanimity strengthens the capacity to savour pleasant experiences and relate to the environment with kindness and compassion, which catalyses the development of well-being [179].

26. Psychological Theories of Mindfulness

When Jon Kabat-Zinn developed the MBSR-course, he decided that he needed to provide a working definition of the complex term *mindfulness*. Very much aware that mindfulness denotes a practice as well as a psychological state during practice and states and traits being the fruit of practice, he offered the following broad definition [206]:

An operational definition of mindfulness is; the awareness that emerges through paying attention on purpose, in the present moment and non-judgmentally to the unfolding of experience moment by moment. (p.145) [206].

Brown, Ryan, and Creswell presented simple definition with complex underlying mechanisms:

“... a receptive attention to and awareness of present events and experiences” (p. 212) [207].

Mindfulness, they argued, concern *clarity* of one's inner and outer worlds. In addition to the clarity of perception, mindfulness also concerns a *non-interference with experience*, by allowing all input to enter awareness. Another key feature is the *flexibility of attention*, and they conclude that when mindfulness comes to full fruition, attention and awareness is regulated in a deliberate and fluid way. Furthermore, mindfulness is characterized by *stability* and *continuity* of attention and awareness. Finally, mindfulness is oriented toward the *present moment*

Shapiro, Carlson, and Astin synthesized a model of how mindfulness contributed to positive psychological change, in which three facets of the mindfulness process are proposed to interact in a cyclic, simultaneous, and seamless way. According to Shapiro et al. mindfulness emerges from a unique combination of *intention*, *attention*, and *attitude*, which catalyse positive psychological change through a number of different mechanisms, including self-regulation skills, value clarification, cognitive- and behavioural flexibility and exposure to distress which leads to the development of tolerance [208].

In 2011, Hölzel et al. reviewed the support for these proposed mechanisms of action in the neuropsychological literature, and complemented the proposed mechanism by the addition of *body awareness*, lacking in earlier theories, and a *change in perspective on the self*, that echoes the core principle in Buddhist psychology [209]. Hölzel et al. agree with Shapiro et al. that the proposed mechanisms of action are interrelated and mutually strengthening, and the whole process could be called *self-regulation*. Their list of mechanisms contains: 1) Attention regulation, 2) Body awareness, 3) Emotion regulation, and 4) Change in perspective on the self.

How these psychological processes translate into increase psychological well-being and decreased psychological distress is a much-debated question, and various groups emphasize different aspects of the mindfulness construct. It is not always clear if they write about the same or different processes. Independent of what psychological mechanisms of action are suggested, research from neuropsychological studies suggest that deliberate practice of various mindfulness exercises induce specific psychological traits that with time and repeated practice, can develop into more stable traits [210]. It has been proposed that the journey from beginner to expert could be characterized by three roughly divided stages; an early stage where the practice takes continuous effort, through a middle stage when effort is needed intermittently to reduce mind wandering, to an advanced stage where mindful attention has become effortless and natural [210].

Creswell and Lindsay have proposed a *Monitor and Acceptance theory of mindfulness* (MAT), which emphasise the *monitoring* aspects of attention and awareness, and the *acceptance* aspect of relating to experience [211]. Recently, they have also provided preliminary evidence that increased skills in both domains are necessary to improve self-regulation and psychological well-being [212]. Interestingly, Lindsay et al. also showed recently that the training of both monitoring and acceptance skills, but not monitoring alone, was associated with reduced cortisol- and systolic blood pressure reactivity in a laboratory setting [213].

Garland et al. connected the process of mindfulness with a theory of positive emotions, which postulates that positive emotions create psychological well-being through an opening up of attention to possibilities in the surrounding environment [214]. They have crafted a *Mindfulness-to-Meaning Theory* (MMT), which emphasize the *reappraisal process* that comes from a decentring from a stressful experience and shift to a broader attention to novel information. This, in turn, accommodates a reappraisal of life circumstances in way that motivates value-driven behaviour and an increased sense of meaning.

Van Der Velden et al. reviewed the literature of studies of MBCT in the treatment for MDD that include measures related to proposed mechanisms of action [215]. The authors found evidence for a significant contribution from *alterations in mindfulness, decreased rumination, decreased worry, increased compassion and improved meta-awareness*. Also, *alterations in attention, improved emotional reactivity and momentarily positive and negative affect* could potentially be involved. The authors conclude that studies with more rigorous design are needed for inferences of causal specificity in these proposed mechanisms [215].

Hayes et al. explained the process of mindfulness in a similar fashion but dressed it in a language that differs a lot from other psychological theories. The ACT-view of mindfulness is grounded in a theoretical stance called *Relational Frame Theory* (RFT), which hypothesize that psychological well-being and adaptive behaviour is often constrained by specific types of learned cognitive biases, including our limiting use of language. These biases are termed *cognitive fusion*, which can lead to *experiential avoidance* and *psychological rigidity*, which in term fuel all types of psychopathology and also very much “normal” behaviour that contribute to suffering in the long run. Based on RFT, the therapeutic technique of ACT was created, and the practices aim to *defuse* the cognitive fusion, and to *open up to experience* instead of avoidance [174].

When treating patients with ACT, therapist catalyse positive behavioural change through the encouragement of value clarification and behavioural activation, and rapid change in perspective are fostered through the use of metaphors and dialogues about how patients relate to their private experiences. Although ACT-therapists not always teach patients to practice mindfulness as a formal meditation technique, mindfulness is a central concept that is theorized to facilitate at least four of the six treatment processes (*contact with the present moment, acceptance, defusion, and self-as-context*). The remaining two treatment processes are *value-clarification* and *committed action*. Together these interrelated processes are hypothesized to increase *psychological flexibility* or a broad repertoire of behaviours that are functional and adaptive in the patient's context and decreases in *experiential avoidance*, which represents the hallmark of psychopathology [216].

The above reviewed proposed mechanisms for how mindfulness works have gained some support from studies with a qualitative design. Malpass et al. reviewed the qualitative mindfulness literature and synthesized a model of how the therapeutic process might work [217]. The model contained three phases: 1) *Perceived safety* - patients benefit from the group setting a sense of normalizing and getting motivated. During this phase, they also expose themselves to how it feels to practice, confront what comes up, and try to let go of striving and expectations. 2) *Safe uncertainty* – patients

begin to transform their experience by developing new ways to relate and calibrate their perspective. 3) *Grounded flexibility* – patients are transforming their experience of suffering or illness by increased skills in self-regulation, sense of control, acceptance, kindness, embodiment, response flexibility and taking action. Participants also reported benefiting from the group setting by a reduced sense of stigmatization and isolation.

Studies with qualitative design could be of great value for the exploration of feasibility and acceptability of mindfulness interventions in a specific clinical context. Since many qualitative methods make use of an inductive, “bottom-up,” process of letting the data inform theory, they have the potential to provide critical views of mindfulness that questions assumptions and premature confidence in the universality of the interventions.

A NOTE ON THE SOCIAL FACETS OF MINDFULNESS-BASED INTERVENTIONS

The fact that both MBSR and MBCT are group interventions, is clinically viewed as an asset, but scientifically it provides challenges for the possible conclusions to be drawn from intervention and effectiveness studies. In an attempt to address these challenges, a group of researchers connected to Richard J. Davidsons laboratory in Madison Wisconsin, have designed a tailored active control condition that is similar to MBSR in format and amount of time spent on various exercises but without the mindful awareness practices of meditation and yoga [218].

From a clinical-practical point of view where we are focused on helping a particular patient to avoid having another myocardial infarction, we might view the multifaceted nature of MBIs as a strength. From this perspective we might be less interested if the stabilization of his or her atherosclerotic plaque is the result of the statin pill, the loosening of a few pounds of overweight, of the cutback of number of cigarettes or cans of beer, if it comes from his newly developed skill to observe his desire to yell at family members without acting on it, or if it comes from the comradeship with fellow MBSR-participants. Furthermore, for some participants a chance to expose themselves to a social context they might usually avoid could be immensely valuable. There are also some themes in the course that directly address attuned- and affirmative communication that could translate into real improvements in interpersonal skills and improved close relationships over time. In a pilot RCT, Creswell et al. showed that MBSR reduced loneliness and down-regulated heightened expression of pro-inflammatory gene activity (NF- κ B-related gene expression in circulating leukocytes), in a group of elderly participants [219].

Here it could be illuminating to remember that most of the studies of psychological interventions for CHD patients, that had found an effect on cardiovascular outcome, was group-based. This fact, in combination with our knowledge of the beneficial effects of social support, and the promising cost-benefit ratio of group interventions, provides further arguments for launching a feasibility trial of mindfulness training for CHD patients with depressive symptoms, which was our aim with *Study III*.

27. The Evidence Base for Mindfulness-Based Interventions

PSYCHIATRIC SYMPTOMS

The literature on the salutary effect of MBIs on psychiatric disorders and their symptoms have recently been reviewed and analysed by Goldberg et al. They found 142 randomized clinical trials and pooled the results from 12005 participants. The disorders included were; addiction, anxiety, depression, pain, schizophrenia, and weight/eating disorders. MBIs were compared to no treatment, minimal treatment, non-specific active control, and specific active control, and evidence-based treatment (mostly CBT). MBIs were superior to no treatment and both control conditions, and equally effective as minimal treatment and evidence-based treatment. When analysing subgroup of patients the evidence was most robust for depression, pain and substance dependency, and the authors conclude that MBIs holds promise as evidence-based treatments [220].

In another recent meta-analysis, which limited its scope to the acute phase of psychiatric disorders, Hedman-Lagerlöf et al. found considerable weaker evidence for MBIs. Drawing on results from a meta-analysis of 19 trials, they concluded that MBIs have weak or no support for effectiveness in the acute phase [221].

CHRONIC SOMATIC SYMPTOMS

The literature on the beneficial effect of MBIs on various symptoms among chronic somatic disease patients was systematically reviewed and analysed by Gotink et al. They included both 23 review articles and 115 RCTs, and analysed the pooled results from 8683 unique individuals. The authors found that MBSR and MBCT, compared to wait-list controls and treatment as usual, significantly improved depressive symptoms and anxiety, perceived stress and quality of life, as well as physical functioning. They concluded that the evidence reviewed supports MBIs as adjunct treatments to alleviate symptoms in patients with cancer, cardiovascular disease, and chronic pain [222].

Goyal et al. performed a similar literature review and meta-analysis and included only RCTs with active controls. They analysed data from 47 trials, and 3515 participants, and found that MBIs had moderate evidence to improve anxiety, depression, and pain, while the evidence for improvements in stress and quality of life was low. Furthermore, they found no effect or insufficient evidence of any effect on positive mood, attention, substance use, eating habits, sleep, and weight [223].

Weight together, the current evidence base for the effectiveness of MBIs to alleviate psychological distress in both somatically ill and psychiatric populations, lend support to the decision to conduct a feasibility trial with MBSR for CHD patients with depressive symptoms.

28. Mindfulness in Coronary Heart Disease

Shortly after the turn of the millennium, the number of published studies with mindfulness in the title or abstract raised exponentially from a handful at the beginning of 1990s to over 300 a decade later, and almost 1000 annually in 2010 [224]. A corresponding explosion in interest in the public sphere has paralleled this exponential rise in published studies on the topic of mindfulness, and the number of newspaper articles reached 34000 around 2015 [225]. Before we move on and review the current state of evidence for MBIs in the specific CHD context, we need to pause around 2010 and briefly consider the state of affairs at this point. This happens to be when the planning of *Study III* and *IV* in this thesis began to take form, sprung from a discussion at a Christmas party between the author and one of the co-supervisors.

When Grossman et al. reviewed the literature and performed a meta-analysis in 2004, they found 64 empirical studies, but only 20 was judged to have adequate quality [226]. The authors concluded their results, although derived from a small sample, suggested that MBSR might help a broad range of individuals to cope with their clinical and non-clinical problems. In the article, they write that the included studies covered a broad spectrum of clinical populations, including pain, cancer, heart disease, depression, and anxiety. Interestingly, the reference to a study of CHD patients was made to unpublished data from Williams et al. (2001), which has not been published since then. When our research group was planning the pilot and feasibility study of MBSR for CH -patients with depressive symptoms, Fjordback et al. published a systematic review of MBSR and MBCT studies in 2011. They found 72 studies and included 21 with adequate quality. Their conclusions were similar to Grossman et al. and they wrote that evidence supports that MBSR improves mental health [227].

During this period, a number of pilot-studies with biological outcome measures were published which provided further encouragement that MBSR might benefit certain patients in the CHD population. Fang et al. published preliminary evidence for an increase in Natural Killer Cell (NK-Cell) activity, and decreased circulating CRP levels, if depression was improved [228]. These findings were intriguing; following the fact that atherosclerosis is first and foremost an inflammatory condition. Hölzel et al. published preliminary evidence for decreased grey matter density (i.e., the thickness of neurons) in the limbic structure of amygdala in 26 healthy but previously stressed subjects [229]. Matousek et al. published preliminary evidence for improved cortisol regulation (measured as cortisol awakening response) among a group of breast cancer patients [230].

During the three years needed for screening and inclusion of patients, and then conduct the pilot trial and collecting 1-year follow-up data, the mindfulness literature grew exponentially. By unknown reasons, the interest among psychologists and cardiologists, interested in the CHD population with psychological distress, was rather cold. In recent years, a handful of studies of mindfulness in the CHD context has emerged and provided both encouragements for further studies but also showed where there are still significant gaps in our knowledge.

The first published trial of mindfulness training for heart disease patients was not with CHD patients but with a heart failure population. In 2007, Sullivan et al. published a prospective cohort study of 208 patients with heart failure (LVEF of ≤ 40 %) [231]. Patients were geographically divided into group treatment or control groups. Patients in the treatment arm met weekly for eight 2.25 h sessions, and besides MBSR-inspired mindfulness training, they also received training in heart failure coping skills (e.g., diet, exercise), and expressive support group discussions. The treatment group had significantly improved symptoms of heart failure at one year follow up, and their CES-D scores decreased very modestly from 21 to 19 at three months and back to 20 at 12

months follow up. However, there were no treatment effects on death or rehospitalisation at 12 months [231]. These mixed results were received with enthusiasm among in some corners of the field of behavioural cardiology, and a few authors advocated further trials with other relevant endpoints, such as inflammation, heart-rate variability (HRV), arrhythmias, myocardial infarction and mortality [232].

In 2012, Nyklicek et al. published their results from a randomized pilot trial of a brief 3-week MBSR-inspired intervention for CHD patients who had underwent a PCI-procedure. The control group received a mindfulness booklet (minimal control) [233]. Compared to the control condition, the brief mindfulness intervention showed larger improvements in depression, anxiety, and mindfulness, but only for participants younger than 60 years old. In this pilot study, no follow-up longer than post-treatment was reported.

In 2013, Parswani et al. reported findings from a study of 30 male patients who had been randomized to either MBSR or treatment as usual [234]. It showed that all patients completed the intervention and significant improvements in perceived stress, depression, anxiety, blood pressure and BMI was seen, and improvements remained at three months follow-up. They concluded that these results prove that MBSR is effective. There are, however, a few methodological uncertainties in this pilot trial. Firstly, the mindfulness training was delivered individually to patients during 1-1.5 h sessions, which mean that the intervention is not comparable to MBSR as it taught in other settings around the world. Secondly, the authors refer to references from the MBCT literature and describe practices, such as the 3-min breathing space, that is included in MBCT but not MBSR. Furthermore, the individual practice session seems to exclude the yoga practice altogether. Thirdly, almost half of the population was lost to follow-up at three months. The authors did, however, reported data on adverse events (none), which is often lacking in the mindfulness literature.

In 2014, O'Doherty et al. published their results from a controlled trial of MBCT for patients with CHD and depressive symptoms [235]. Thirty-two patients were assigned to MBCT and 30 patients allocated to a wait-list control group. Both groups were followed up after six months. The authors reported that 71 % of the patients in the MBCT-group recovered from their depression (a score below eight on the HADS depression subscale), compared to 50 % in the control group. The MBCT group also showed greater improvement in anxiety, mood, coping with illness and a mindful awareness scale. Although this study remains the central point of reference for *Study III* in this thesis, it had an important limitation. The trial had a large dropout rate (47 %), and the authors attribute this to a high prevalence of ambivalence among patients, and that some might have attended a few sessions to comply with the advice of their cardiologist. They also speculate that the stigma around psychological distress and psychological treatment, still prevalent in Ireland, might have contributed to the large dropout rate.

In addition to these clinical pilot trials of patients with CHD, Louks et al. have shown that dispositional mindfulness, measured with the Mindful Attention Awareness Scale (MAAS), was associated with cardiovascular health. In a cross-sectional study of 382 subjects (mean age 47 years), dispositional mindfulness (dichotomized into high vs. low) had a prevalence ratio of good cardiovascular health of 1.83 (CI 1.07-3.13), when adjusted for age, gender and race/ethnicity. They also showed that dispositional mindfulness correlated with smoking habits, body mass index (BMI), fasting glucose level, physical activity, but not blood pressure, blood lipids or fruit and vegetable consumption. Further mediation analysis suggested that sense of control and depressive symptoms might have mediated the observed associations [236].

29. Mechanisms Linking Mindfulness Training to Coronary Heart Disease

Louks et al. also provided a theoretical framework with plausible mechanisms for how mindfulness training could benefit CHD patients [237]. In their conceptual model they provided a psychological framework that echoed our discussion above with a cyclic, interrelated dynamic process of improved *attention control*, *emotion regulation* and *self-awareness*. These processes interactively lead to improved *self-regulation*, which in turn have a positive influence on *health behaviours* and their downstream consequences (e.g., smoking, physical activity, diet, BMI, blood pressure, lipids, glucose), and on *direct pathways* related to CHD risk, like *heart rate variability* (HRV) and *inflammation*. The authors link their model to current neuropsychological findings and stress biology and highlight the same usual suspects we have reviewed in this introduction; anterior cingulate cortex (*attention control*), amygdala and its prefrontal cortex inhibition (*emotion regulation*). They elaborate further on psychosocial mechanisms like *self-efficacy* and *sense of control*, *social support*, *value clarification*, *body awareness* and *present moment awareness*, which are all familiar constructs for us by now, and cite evidence for an impact on these factors from mindfulness. The authors conclude that there is promising but still inconclusive evidence for associations between mindfulness training, and CHD risk and they warrant more trials and studies that could identify which patients are most likely to benefit from mindfulness interventions and explore how MBIs could be customized to fit target populations. What is not entirely clear in Louks et al.'s model of plausible mechanisms is *how* the proposed psychological changes are linked to the biological pathways (e.g., the stress response and inflammation). Here, the scientific evidence is somewhat scarce and more or less plausible hypotheses are more abundant.

Creswell and Lindsay, elaborated on this question in a review article and proposed that the health benefits of mindfulness training come from a stress-buffering effect [238]. Grounding their reasoning in evidence for biological pathways that has been shown to be influenced by, or correlate with, mindfulness training, Creswell and Lindsay, highlighted 1) the recruitment of prefrontal regulatory regions in the brain, that may inhibit activity in “lower” stress processing regions (e.g., the amygdala), “top-down” regulation; and 2) direct effects on the stress processing regions, “bottom-up” regulation. These alternations are then hypothesized to affect peripheral physiological stress response cascades, in the ANS and the HPA-axis. Decreased activation of the stress response in the peripheral nervous- and immune system could influence disease-specific pathophysiological pathways. In our CHD context it is suggested that increased sympathetic tone in the ANS, and altered or disrupted activity in the HPA-axis, can negatively influence the atherosclerotic disease process. When it comes to the “missing link” between psychological traits and states” and changes in biological pathways (including the brain), Creswell and Lindsay, suggested that mindfulness:

“... facilitates a capacity to receptively observe stressors as they arise, with acceptance and equanimity, which in turn buffer initial threat appraisals and increases secondary appraisals of coping resources.”
(p.5) [238]

With this proposal, the authors provide a possible connection between a transformation of stressful experiences and the subsequent building of psychological resources. In their conclusions, Creswell and Lindsay added an important caveat that might have major implications for future studies in the field of behaviour cardiology, namely that there might be a flipside to the stress-buffering view of psychophysiological processes. They admit that it might be possible that mindfulness training could have direct effects on positive psychological states, which in turn impact health via anabolic processes.

There are broad and profound questions that researchers should ask, and investigate empirically, that are connected to the possibility of a truly “positive” view of both psychology and physiology. Could health-building psychobiological processes and pathways go beyond, or through other routes, than the stress response systems? If so, what psychological traits and states are responsible for activation and integration of these *positive biological pathways*? Moreover, how is these psychological processes linked to biological pathways and health sustainability?

Researchers in the fields of positive psychology and psychoneuroimmunology have indeed addressed variants of these questions, but very few studies that directly investigate them have been carried out. Even when researchers study positive traits like e.g., optimism and, sense of meaning, they tend to frame there questions and answers in a stress-buffering framework. A notable example is the growing interest in the concept of *resilience*, which refers to the capacity to maintain mental health despite exposure to psychological or physical adversity [176]. Resilience researchers argue that their framework aims at understanding protective mechanisms instead of focusing on the pathophysiology of stress-related disorders. However, in the end, they frame their theories and results within the same stress-buffering rationale as the traditional science of psychopathology.

Of course, the questions posed inside the stress-buffering framework are immensely important, and millions of people could benefit from more effective ways to promote resilience among people facing adversity (which would be most of us). However, this view is inherently limiting, and there are exciting possibilities that a thorough exploration of positive psychobiology could lead to novel ways to create bio-psycho-social sustainability, and prevention of diseases, that are unknown to us today.

Early and pioneering studies of *positive psychobiology*, have provided some intriguing preliminary evidence of unique biological correlates to positive psychological states and traits. For example, positive affect has been linked to greater relative activation of left-sided prefrontal cortex activity [239], which in turn has been shown to predict NK-cell activity. Positive mood has been associated with increased levels of specific circulating cytokines, e.g., IL-2 and IL-3, while the more pro-inflammatory cytokines INF-Alpha and TNF-Alfa, are decreased. Studies of positive traits and states such as empathy, which links the psychological level to both the social and biological, has revealed associations to parts of the prefrontal cortex (e.g., ventromedial), and that neuropeptides such as oxytocin and vasopressin are associated with increased trust and cooperation and to activation of reward circuits in the brain [240].

Although some of the above mentioned biological systems could represent uniquely “positive” pathways, other systems have considerable overlap with the structures and systems that mediate the stress response. These include the prefrontal cortex and the amygdala, which are involved in the processing of both negative and positive affect [241]. In the end, we will have to recognize that concepts like “negative” vs. “positive” and “pathophysiology” vs. “normal” physiology, is cognitive scaffolding we use when we study and communicate these phenomena. A living organism manage to orchestrate an “upstream” journey against the underlying trend of increased entropy in our universe, and often manages to perform this marvellous trick by the interconnected and integrated activity of physiological systems of regulation that have evolved during a couple of billion years of incremental steps toward adaptation. Viewed from an evolutionary perspective, it becomes clear that the structures and systems involved in both the stress response and more anabolic and repair-oriented processes were shaped to enhance the chances of survival and reproduction, which could be translated into social, psychological and biological sustainment and health.

30. Critique of Mindfulness Research

Although we now can count the number of clinical trials, testing mindfulness-based interventions in various contexts, in the range of hundreds, there are still large gaps in our knowledge, and the research to date has not been spared critique. In reviews of mindfulness, its mechanisms, and its utility, authors are often quick to admit that the science of mindfulness is still in its *infancy* [224]. However, if we compare where the theoretical work and the clinical evidence stand today, it could be more accurate to say that mindfulness research is in its *adolescence*. Today, the mindfulness movement has the unique combination of hubris and insecurity of itself that is common in adolescence, and there is a fair amount of debate around the issue of identity that hopefully could lead to some form of maturation into an adult science of contemplative psychology.

Recently a group of 15 mindfulness teachers, researchers, and Buddhist scholars published a critical article called “Mind the hype,” in which they warned that misinformation and methodological shortcomings in the mindfulness literature could lead public consumers to be harmed, misled and disappointed [242]. The authors present a rather exhaustive list of interconnected difficulties with the present state of evidence and provides suggestions for moving the field in a more sober direction. First, they elaborate on the much-debated meaning of the word *mindfulness* and connect the diversity of definitions to subsequent difficulties with assessing the construct. They express scepticism that anyone theoretical model can explain and predict all phenomena stemming from mindfulness practice and mindfulness skills. The authors also highlight various definitions of who is a novice or an expert or adept at practicing mindfulness and problematize that some proponents, especially in ACT and DBT, do not require any systematic training at all [242]. They also recognize that researchers often use self-report measures of mindfulness and warn that these might measure skills and vulnerabilities that are not specific to the trainings, states, and traits of mindfulness. The solution, they advocate, is to redirect focus from attempts to directly measure mindfulness, toward measuring supporting mental faculties and study these phenomena from a variety of angles; social, emotional, cognitive, behavioural and biological.

The authors move on to address clinical trials and conclude that too few efficacy studies have been carried out with active control and that only 1 % of clinical studies have been conducted outside of research context, highlighting a gap in knowledge about the readiness of MBIs to be used in clinical practice. They continue by citing some of the latest meta-analysis of efficacy (including Goyal et al. 2014) and conclude that much more research will be needed before we know for which mental and physical disorders MBIs are definitively beneficial. The authors summarise their article by raising the underappreciated issue of adverse effects from participation in MBIs. They describe potential risks such as autonomic hypoarousal, perceptual disturbances and relaxation-induced panic or anxiety, and suggest that adverse events (AEs) should be reported in all clinical trials and that mechanistic studies could inform this topic [242].

Wong et al. recently investigated the safety issue of MBIs and who conducted a literature review and performed a meta-analysis of MBSR and MBCT studies that reported AEs [243]. The authors found 36 RCTs and compared the number of AEs in the active treatment groups compared to control groups. In MBSR groups there were no serious adverse events and six intervention-related adverse events among 1231 participants. There was no significant difference between the MBSR and the control group (risk difference 0.0033 CI -0.01 – 0.01). In the MBCT group, no intervention-related adverse event was reported, and only one trial reported ten intervention-unrelated-adverse events from 768 participants. No statistically significant difference in comparison to the control groups was seen. The authors conclude that in general, only a small proportion of trials reported monitoring of adverse effects. Very few adverse events were reported in the RCTs and the suggest

that MBSR and MBCT should be regarded as relatively safe interventions [243].

Another type of critique against the whole “mindfulness movement” was collected into an anthology called “Handbook of mindfulness – Culture, context and social engagement,” by Purser et al. and published in 2016 [244]. A long list of authors with various backgrounds and views presents a critique of the western adaptation of Buddhist practices under the vague umbrella term mindfulness. According to these critical voices, the current mindfulness movement is downplaying question of ethics, so central to the Buddhist world-view, and from this comes an under-appreciation of the social consequences of the Buddhist core ideas of *selflessness*, and the imperative to practice compassion. Some authors argue that the focus on individual improvement in awareness and presence directs attention to the individual as the responsible agent for psychological well-being, and subsequently away from social and societal sources of distress, such as inequalities. This individualistic focus links the mindfulness movement to similar shortcomings of the broader self-help movement and the psychotherapy business. Others contend that the application of mindfulness programmes in corporate settings could quietly lend its utility to the productivity and efficiency goals of these organizations, and thus connect the mindfulness movement to the broader context of the capitalist structure.

Finally, some commentator, e.g., the psychoanalyst and Buddhist teacher Mark Epstein, have warned that the use of mindfulness as a therapeutic technique in its own right, without the larger context presented by the Buddhist view, could lead to unrealistic expectations and difficulties seeing the real value of the practices [245]. Indeed, in the Buddhist system of thought, *right mindfulness* is only one part of the eightfold path (the other seven being; *right view*, *right intention*, *right speech*, *right action*, *right livelihood*, *right effort* and *right understanding*).

According to what we do know about mindfulness interventions in general, and what gaps remain after a handful of pilot trials have been carried out in the context of CHD we have a quite convincing case. Against this background we can argue for the soundness of trying the mindfulness-based intervention that was developed for chronically somatic ill patients (MBSR), for the CHD patients with elevated levels of psychological distress. This was the aim of *Study III*, and *Study IV* expand the basic feasibility question to also address how participant’s experience the mindfulness practice and thus, what this experience tell us about barriers to and benefits from learning mindfulness and yoga as a complement to cardiac rehabilitation.

MATERIAL & METHODS

31. The Life conditions, Stress and Health Study (*Study I & II*)

STUDY DESIGN, PARTICIPANTS AND PROCEDURES

The aim of *Study I* was to investigate if the use of inverted items in the self-report instruments Self-esteem, Mastery, and CES-D (depressive symptoms), represent a validity risk when the questionnaires were used in the context of CHD. The aim of *Study II*, which was performed before *Study I*, was to investigate if psychological resources and risk factors were independently associated with incidence of CHD.

Study I and *II* were both based on data from the LSH population, a sample of 502 men and 505 women aged 45–69 years, randomly drawn from the Swedish Population Registry, which includes all habitants in the county of Östergötland, Sweden. Exclusion criteria were severe physical- (e.g., terminal cancer or dementia) or psychiatric illnesses interfering with study procedures. Baseline data collection was conducted in 2003 and 2004. Participants were invited to visit their Primary Health Care Centre. They filled out a set of questionnaires, covering demographic information, health behaviours, self-report instruments for psychosocial resources and risk factors, as well as previous and present disease. During the visit, a short vital status was taken and fasting blood samples were obtained for analysis. The response rate was 62.5 %, and the sample was representative of the general population regarding the level of education, employment status, and immigrant status.

To address the research question in *Study I*, both cross-sectional data from self-report questionnaires (CES-D, Mastery, and Self-esteem) (n=1004) and IL-6 (n=374) and longitudinal data of 8-year incidence in CHD (n=1000) were used. *Study II*, which investigated independent associations with the eight-year incidence of CHD, had a *prospective* or *longitudinal cohort study* design, with CHD disease incidence as a primary outcome.

DEMOGRAPHIC FACTORS, HEALTH BEHAVIOURS, AND PHYSIOLOGICAL CORONARY HEART DISEASE RISK FACTORS

In *Study I* and *II*, information about participant's demographic characteristics (age and sex), as well as health behaviours and physiological CHD risk factors were collected at baseline. The habit of smoking was dichotomized into the two groups *smokers*, including those who had stopped in the last five years, and *non-smokers*. Physical activity was calculated as an index of the weekly sum of structured physical exercise and everyday physical activity and then divided into four groups according to guidelines [246]. Intake of alcohol was divided into five groups; *no intake* (0g/week), *low to moderate* (0.1-80g/week), *high* (81-160 g/week) and *very high* (>160g/week) and *quit drinking* [247]. Intake of fruit, vegetables, and nuts was assessed with a validated food-frequency questionnaire [248]. Adequate intake was defined as *high* (>500g/week) or *low* (<500g/week). Body Mass Index (BMI) was calculated from height and weight, and was used as a continuous variable. Blood pressure was measured three times in a sitting position, in two-minute intervals after 5 minutes of rest, using the mean of the second and third measurement (Omron M5-1, Digital). Fasting blood lipids (total cholesterol, HDL, and triglycerides) were analysed with ADVIA 1650 apparatus, and LDL was calculated with Friedewald's formula [249]. Presence of diabetes mellitus diagnosis was measured with a question in the self-report questionnaire.

PSYCHOLOGICAL MEASUREMENTS

All psychological self-report instruments used in *Study I* and *II* were introduced in chapters 16-18. *Symptoms of depression*, a variable assessed in all four studies, was measured with the CES-D scale [75]. The instrument contains 20-items with four alternative answers, and the scale ranges between 0-60 points.

Vital exhaustion measures a combination of mental and physical fatigue and was assessed with a 19-item self-report instrument [118] and used as an outcome measure in *Study II*. The scale ranges from 19-57 points.

Hopelessness measures a negative orientation towards the future and a lack of hope. It was measured with a two-item questionnaire [124] and was used as an outcome measurement in *Study II*. The scale ranges from 0-8 points.

Cynicism measures a subjective sense of distrust toward other people and was measured with a 12-item scale [116]. It was used as an outcome in *Study II*. The scale ranges from 12-60 points.

Hostile affect measures feelings of hostility towards other people and was assessed with a 5-item questionnaire [116]. It was used as an outcome measure in *Study II*. The scale ranges from 5-25 points.

The 7-item *Mastery scale* measures a sense of confidence in one's ability to handle the challenging facets of life [142]. It was used as an outcome measure in *Study I*, *II* and *III* and thus plays a central role in this thesis. The instrument ranges from 7-28 points.

Self-esteem measures a sense of self-worth and a trust in one's competences [139]. It contains ten items and was used as an outcome measure in *Study I* and *II*. The instrument ranges from 10-40 points.

The 13-item version of the *Sense of Coherence* (SOC) questionnaire was used as an outcome measure in *Study II*. It measures to which extent life is experienced as comprehensible, manageable and meaningful. [149] The scale has a range between 13-91.

INFLAMMATORY ACTIVITY

The circulating cytokine *IL-6* is a well-studied biological marker of inflammatory activity throughout the body. It has been linked to both risk of CHD [250] and to psychological factors [26]. Plasma levels of *IL-6* was measured with a high-sensitivity sandwich Enzyme-Linked Immunosorbent Assay (ELISA); Quantikine, R&D Systems Inc, Minneapolis, USA. For economic and technical reasons, this analysis was done in 400 randomly selected samples from the LSH-population, and was used as a criterion measure in *Study I*.

INCIDENCE IN FIRST TIME CORONARY HEART DISEASE

First-time major coronary event of CHD was defined as fatal or non-fatal myocardial infarction, or an event of invasive coronary revascularization, defined as percutaneous coronary intervention (PCI) or coronary by-pass-graft surgery (CABG). Data of incidence in coronary events during the 8-year follow-up time was obtained from the Cause of Death Registry and the Registry of Hospital Admissions, covering more than 99 % of hospital discharges in Sweden. The Swedish National Board of Health and Welfare administer both these registries.

PSYCHOMETRIC AND PSYCHOBIOLOGICAL VALIDITY TESTING

In *Study I*, the concurrent and predictive validity, and construct dimensionality, of the self-report instruments Mastery Self-esteem and CES-D, were evaluated. To test construct validity, we divided the three original scales into subscales containing only positively and negatively worded items. The items from these three self-report instruments are presented in Appendix A (page 110).

Concurrent construct validity is considered supported if the scores of an instrument are correlated with a related criterion at the same point in time [251]. Convergent construct validity is supported if there is a clear overlap between constructs that are theoretically similar (e.g., Mastery and Self-esteem) [251].

To test *concurrent construct validity* (criterion a), the three original scales and the six subscales were analysed in relation to other scales with an expected negative outcome (CES-D for the resources and the resources for CES-D). Thereafter (criterion b), the nine scales and subscales were analysed in relation to IL-6.

Predictive validity is supported if a measure is able to predict an outcome that has a known theoretical or empirical relationship to the theoretical construct of the instrument. To test *predictive construct validity* (criterion c), Cox proportional hazard ratios for 8-year risk of incidence in CHD were calculated for each of the nine scales and subscales.

Finally (criterion d), *construct dimensionality* was analysed with a factor analysis of the items in the original scales. Interpretation of factor loadings is dependent on the nature of the theoretical construct in question. If it is apparently one-dimensional, ideally all items should load on one component with high factor loadings. If the construct is multidimensional with distinct facets, items are expected to load on a number of different components. However, in multidimensional constructs with closely related facets, items can load on more than one component.

32. The Mindfulness Intervention as Myocardial Infarction Rehabilitation Additive Study (*Study III & IV*)

STUDY DESIGN, PARTICIPANTS AND PROCEDURES

Study III was a clinical trial that investigated if MBSR could be a feasible and acceptable intervention for CHD patients with depressive symptoms after a recent coronary event. A second aim was to study if the intervention had any long-term effects on Mastery and depressive symptoms. The trial had an open design (non-controlled, non-randomized, and non-blinded) with a follow-up time of 12 months.

CHD patients, who were referred to the outpatient clinic of the Department of Cardiology, Linköping University Hospital, Sweden, were asked to fill out the Centre for Epidemiological Studies Depression scale (CES-D) questionnaire one month after their coronary event, i.e., myocardial infarction or coronary revascularization procedures; PCI or CABG. Patients with elevated CES-D scores (using the median as a cut off, which was 8 points, in the reference group, described below) were consecutively identified, and invitation letters for participation in MBSR were sent. Exclusion criteria were major clinical depression (based on physician's clinical judgment), severe comorbidities, such as cancer, severe cognitive impairment, psychosis, and alcohol or drug abuse since these conditions might imply difficulties to complete MBSR. Our cut off of ≥ 8 points on the CES-D scale, resulted in the inclusion of patients with subclinical depressive symptoms as well as mild- to moderate depression. Patients who accepted the invitation were informed via phone about the 8-week MBSR course. We aimed to reach an active MBSR group of 25 participants, as previously recommended and the number of participants that started the course was 24. At the end of the 8-week MBSR course, as well as after the 12 months follow-up period post-MBSR completion, medical charts of the participants (both completers and dropouts) were reviewed for adverse cardiac events (e.g., new acute coronary events). Although primary outcome in *Study III* was various facets of feasibility, psychological resources and risk factors were measured with self-report questionnaires. Measurements were made at three different points in time; before MBSR, immediately after the course and 12 months after completion of MBSR.

A reference population of patients from the same outpatient clinic provided 12-month longitudinal data of depressive symptoms and Mastery. The patients in the reference population had participated in a longitudinal survey of Mastery and depressive symptoms (CES-D). One month after their coronary event, patients filled out the questionnaires. The majority of patients (72 %) returned for a 12-month visit and filled out the questionnaires a second time.

DEMOGRAPHIC FACTORS, HEALTH BEHAVIOURS, AND ESTABLISHED CORONARY HEART DISEASE RISK FACTORS

In *Study III* and *IV*, demographic characteristics (age and sex), as well as waist circumference and index event (MI, PCI or CABG) were derived from participants medical chart. Data of smoking habits (later grouped in the same manner as *Study I* and *II*), use of antidepressants and the presence of the comorbidities hypertension and diabetes mellitus, were derived from the baseline self-report questionnaire, which contained specific items asking for this.

PSYCHOLOGICAL MEASUREMENTS

Study III used Mastery and CES-D, and their characteristics have been described in chapter 32 above. We also used the following battery of psychological measurements:

The 29-item *FFMQ-instrument* was used as a secondary outcome in *Study III*, with the aim of measuring a construct related to the mechanism of change related to the MBSR-intervention. The construct of mindfulness is introduced in chapter 26. The questionnaire, synthesised from five previous instruments by Baer et al. [252], captures five facets of self-reported mindfulness skills; *observing, describing, acting with awareness, non-judgement, and non-reactivity*. The scale ranges between 29-145 points.

The *Acceptance and Action Questionnaire-II (AAQ-II)* contains seven items related to the three theoretical constructs of *acceptance, psychological flexibility, and experiential avoidance*, which are central to ACT and RFT [253]. The rationale for including this scale as a secondary outcome in *Study III* was to capture another potential mechanism of change in mental well being related to the MBSR-intervention. The scale points range between 7-49 points.

The *Generalized Anxiety Disorder-7 scale (GAD-7)*, developed by Spitzer et al. [254] contains 7-items that captures the central symptoms of generalized anxiety disorder, as the DSM-system defines it. GAD-7 was used as a secondary outcome measure in *Study III* as a way to broaden the measure of psychosocial risk factors. The scale ranges from 0 to 21 points.

One central item from the *Karolinska Sleep Questionnaire (KSQ)*, asking for an overall sense of subjective sleep quality [255] was used as a secondary outcome measure in *Study III*. This one-item measurement had a scale range of 0-4 points.

The Ladder of Life is measuring an overall sense of life quality on a visual stepped ladder ranging from 0-10 points [256]. This instrument was used as a secondary outcome measurement in *Study III*. The rationale for the inclusion of this measurement was first and foremost to add a life quality assessment to the arsenal of feasibility outcome, but also as a complementary psychosocial outcome.

FEASIBILITY OUTCOME IN THE MBSR TRIAL

The primary outcome of *Study III* was the feasibility and acceptability of MBSR among CHD patients with depressive symptoms. Since this is both a highly practical issue and a question of subjective experience, six different feasibility outcome measures were used:

- 1) Number of invited, interested, starting and completing participants as well as drop out rate.
- 2) Attendance rate at the weekly meetings.
- 3) Self-reported home practice time.
- 4) Ratings (0-10) of 10 different facets of the MBSR-intervention (Visual Analogous Scale – VAS), and three yes/no questions about overall attitude to the MBSR-course (See Table 4, page 78).
- 5) Effects on psychological variables.
- 6) Adverse outcomes during the 8-week intervention or the 12-month follow-up period.

QUALITATIVE DATA IN STUDY IV

Study IV was a longitudinal qualitative study that analysed written content from training logs (diaries) from 12 of the participants in the intervention group. The recruitment procedure and clinical trial design were the same as for *Study III*.

During the 8-week MBSR course, participants were asked to reflect freely in a prepared diary, for 15-20 minutes after their home practice sessions of meditation and yoga. If the writing did not emerge easily, the participants were encouraged to reflect over one or a few of seven different questions (prompts). These questions were specifically developed to be open-ended and non-directive, and as such directing the reflection to participant's immediate experience after the practice session:

How did you feel during practice?

Did any particular thoughts or stories appear?

Did any particular emotions or moods occur?

Was it pleasant or unpleasant to practice?

How did you handle the pleasant or unpleasant experience?

What are your feelings here and now after the practice session?

Which thoughts appear now when you reflect on your practice session?

33. Data Analyses

Study I and II used Cronbach's alphas (α) to evaluate reliability and to test internal consistency for the three original scales Mastery, Self-esteem, and CES-D. This is usually the method of choice when a scale contains items that are theoretically correlated [257].

Partial Pearson's correlation coefficients, adjusted for age and sex, were used as a means to test concurrent construct validity. Original scales and subscales with only positive- or negative items were tested against each other, as well as in relation to IL-6. In correlation analyses with IL-6, adjustments were, in addition to age and sex, also made for the effects of BMI, smoking, physical inactivity, alcohol consumption, fruit and vegetables intake, blood pressure, blood lipids and diabetes mellitus. To test predictive construct validity, Cox proportional hazard models were calculated for each of the nine subscales in relation to the 8-year risk of first time CHD, with adjustments for; age, sex, blood pressure, blood lipids, diabetes, BMI, smoking, physical inactivity, high alcohol intake and low fruit and vegetable intake. The resulting HR was presented per standard deviation (SD) to allow comparisons across scales with different scale ranges. Principal Component Analysis (PCA), with Varimax rotation, was used to analyse construct dimensionality. An eigenvalue of 1.0 was set as the limit for factor extraction, and a factor loading of > 3.0 as cut off and a 2-factor model was used as restriction.

In *Study II*, Spearman correlation coefficients were used to analyse how psychological resources and risk factors were related to each other. A set of Cox proportion hazard models for each of the psychological factors tested was calculated with the incidence in CHD as the outcome. Adjustments were made in three steps for: 1) age and sex. 2) Age, sex, BMI, smoking, physical inactivity, high alcohol intake and low fruit and vegetable intake, blood pressure, blood lipids and diabetes. 3) All from point 2 plus depressive symptoms as a dichotomous variable. The resulting HR was presented per standard deviation (SD) to allow comparisons across scales with different scale ranges

In *Study III*, Shapiro-Wilks test was used to analyse if data followed the normal distribution or not. Since a few variables were not normally distributed, we used Wilcoxon sign rank test to compare mean values at different points in time. Differences between groups at baseline were analysed with Mann-Whitney U-test, and Chi-2 test was performed for nominal data. Correlational analyses were performed with Spearman correlations.

Statistical analyses in the four papers were made with SPSS for Macintosh versions 21 (*Study II*) and 22 (*Study I and IV*) and 24 (*Study III*).

Study IV was a qualitative study, which used the method of content analysis of participant's diaries. Descriptive statistics (median and interquartile range) were used for participant's background characteristics. The qualitative method of *directed* (inductive) *content analysis* [258] was used when we analysed the content from the 12 diaries from participants in the feasibility trial. Here follows a brief description of the steps in the analytic process. Firstly the texts were read and re-read multiple times to allow immersion. Secondly, key thoughts were extracted as *quotes* ($n=459$). All quotes were coded into more condensed sentences, and the *codes* were tagged with week-number 1-8 (when it had been written down during the MBSR-course). Thirdly, codes were grouped into *emergent subcategories*, and subcategories were organized into *meaningful clusters*. Fourthly, a condensed list of six *subcategories* was condensed into two *categories*, and in the last step, one more interpretative *main category* was derived. In the presentation of our findings, each category was strengthened by a quotation. The rationale for our choice of this method, as well as its advantages and disadvantages, are discussed in further depth in methodological considerations, chapter 40.

34. Ethical Considerations

The recruitment of participants and collection of data, including blood samples, vital status and an extensive questionnaire of demographic, social- and psychological characteristics, from randomly selected subjects from the community, in the LSH-population, was not associated with any major threats to health, privacy or autonomy. Participation was voluntary, and participants received advice about lifestyle and preventive measures as a small reward but were not economically compensated in any way. Written consent was obtained before enrolment, and the Regional Ethical Review Board approved the study. All data was made anonymous, and the code for identification of individual participants was only available to a small number of people in the research group.

The MIMIRA-study, with its open feasibility and pilot trial design, and with the recruitment of patients with depressive symptomatology, poses some ethical questions. First of all, one might ask if the cognitive impairment that often accompanies depressive symptoms (or represents one of the symptoms), could lead to a compromised autonomy for patients who were asked if they were interested in participating in the study. Cognitive impairment could lead to difficulties in the patient's discernment of suitability of the intervention and possibly lead to both acceptance without real conviction and commitment, or to a decline even though there could have been openness for giving MBSR a try. However, these potential threats to autonomy would be inherent in all possible trials of interventions directed at depressed patients, and we decided to address this by providing both written and verbal (phone call) information of what participation would mean, before enrolment. Written consent was obtained before participation and participants were free to withdraw from the study at any time without any further inquiries. There were, at the time, a number of studies of other patient categories with promising results. All patients were also receiving conventional cardiac rehabilitation, so there were no other treatment modalities that were withheld from this group, except participation in other variants of stress-reduction education during the 8-weeks or the follow-up time.

A third potential risk with offering MBSR to CHD patients with depressive symptoms, which could be independent of the actual effectiveness of the intervention, is the possible negative consequences for those who would choose to drop out and not complete the intervention. The emotional costs of investing hope, time and energy into a project that could reduce stress and low mood, and then take the decision to withdraw, could possibly consolidate low self-esteem and lead to feelings of disappointment and hopelessness. We addressed this issue by offering patients who dropped out an extra follow up visit with the cardiac nurse. Participants did not receive any economic compensation, but the MBSR course, including workbook, CD, yoga mat, meditation cushion, tea, coffee, and fruit, were provided at no costs.

In addition to potential ethical issues with the MIMIRA-trial, described above, the MBSR intervention might also offer ethical advantages. When it comes to the treatment of psychological disorders, there are moral dimensions linked with treatment modalities. The bioethicist Paul Biegler has argued that psychotherapy has ethical advantages compared to psychopharmacologic intervention, in such that psychotherapy generates self-knowledge and skills to appraise and manage stressors, and that this represents a strengthening of *autonomy*. Taking a pill that modulates neurogenesis and the reuptake of monoamines in the brain does not offer the same autonomy-boost but could instead create a sense of dependency and cement a limiting view of patient's lack of recovery potential [259]. Indeed, one could argue that mindfulness training goes one step further than individual psychotherapy, since participants in an MBSR course is conquering his or her improved skills in attention- emotion- self- and behaviour regulation through laborious practice on the meditation cushion and on the yoga mat. These efforts are guided and supported by, but not

dependent on, the teacher. This, one could argue, represents an even greater strengthening of autonomy since the individual receiving training in mindfulness becomes empowered to trust his or her skills once the intervention is finished.

Some proponents of mindfulness-based intervention have argued that the practice of meditation implicitly fine-tune participants pro-social tendencies, while others warn that there are ethical disadvantages with treatment modalities that have their roots in one of the world religions, since this could lead to feelings of cultural discomfort among some participants [260]. Furthermore, a respect for cultural diversity is stipulated in most professional ethical codes, which warrant caution when introducing methods with this kind of historical and cultural framing.

The method of collecting written content from diaries in *Study IV* raised ethical considerations regarding confidentiality and identification of individual participants. We addressed these issues by limiting the availability of the notebooks to only one researcher, and all written content was made anonymous before the analytic process began. Participants were informed about the potential publication of quotes and data from the training logs, both in the written consent form, and again reminded about this in the writing instruction in the prepared notebooks, explicitly instructed not to write anything they wanted to keep entirely private.

RESULTS

35. Inverted Items and Validity (*Study I*)

The two resource scales showed a two-factor structure in the factor analysis, but there was significant overlap among individual items, suggesting that they measure the same or closely related facets of the construct. We found no differences between positive and negative resource subscales and the original scales in their relationships to CES-D (see the article from *Study I*), plasma levels of IL-6 or 8-year CHD risk (Table 1 and Table 2).

Table 1. Results *Study I*: Partial Pearson Correlations between the original scales and subscales of psychological factors with IL-6. Results after adjustment for possible confounders ^a, *n*=374.

	IL-6 (pg/ml)	<i>p</i> -value
Self-esteem	-0.16	0.002
Self-esteem Pos	-0.13	0.014
Self-esteem Neg	-0.16	0.003
Mastery	-0.16	0.001
Mastery Pos	-0.14	0.006
Mastery Neg	-0.15	0.003
CES-D	0.19	<0.001
CES-D Pos	0.05	0.280
CES-D Neg	0.26	<0.001

^a Adjusted for age and sex, BMI, smoking, physical inactivity, alcohol consumption, fruit and vegetables intake, blood pressure, blood lipids and diabetes mellitus.

The results for the CES-D scale, on the other hand, showed a divergent pattern for the subscale with four positive items, as these did not correlate with IL-6, or CHD risk (Table 1 and Table 2). Furthermore, the factor analysis did not show any overlap in loading on the two components, whatsoever, between the positive and negative items of CES-D (Table 6, manuscript of *Study I*).

Table 2. Results *Study I*: Cox Proportional Hazard Ratio (per SD) for 8-year CHD risk after full adjustment for possible confounders^a, *n*=1000.

	SD	HR/SD	CI (95%)	<i>p</i> -value
Self-esteem (<i>n</i> =806)	4.79	0.62	0.47 - 0.83	0.001
Self-esteem Pos (<i>n</i> =796)	2.46	0.65	0.48 - 0.89	0.007
Self-esteem Neg (<i>n</i> =777)	2.95	0.64	0.48 - 0.85	0.002
Mastery (<i>n</i> =809)	3.42	0.64	0.47 - 0.87	0.004
Mastery Pos (<i>n</i> =801)	1.26	0.68	0.50 - 0.91	0.010
Mastery Neg (<i>n</i> =795)	2.76	0.70	0.52 - 0.94	0.018
CES-D (<i>n</i> =803)	7.86	1.46	1.11 - 1.93	0.007
CES-D Pos (<i>n</i> =796)	3.46	1.14	0.83 - 1.57	0.404
CES-D Neg (<i>n</i> =752)	5.80	1.50	1.17 - 1.92	0.002

^a Adjusted for age, sex, BMI smoking, physical inactivity, alcohol consumption, fruit and vegetables intake, blood pressure, blood lipids and diabetes mellitus.

36. Psychological Risk Factors and Resources and 8-year Coronary Heart Disease Risk (*Study II*)

Eight years after baseline data were collected, 56 out of 1007 participants had suffered an acute coronary event. Our analyses showed that after adjustment for all the traditional risk factors, a significantly decreased risk was found for the resources Mastery (HR 0.62 per SD, CI 0.46-0.85), Self-esteem (HR 0.62 per SD, CI 0.47-0.86), and Sense of coherence (HR 0.70 per SD, CI 0.51-0.96). Please see Table 3 below.

As expected, the risk factors were associated with an increased risk of CHD; depressive symptoms (HR 1.45 per SD, CI 1.09-1.92), Vital exhaustion (HR 1.46 per SD, CI 1.09-1.92) and Hopelessness (HR 1.59 per SD, CI 1.16-2.17). Cynicism and Hostile affect were not significantly associated with CHD in this model (Table 3).

When we added depressive symptoms (CES-D-scores), as an additional adjustment variable, we found that the associations remained for Mastery, Self-esteem, and Hopelessness, but not for Sense of coherence and Vital exhaustion (Table 3, Model C).

Table 3. Results *Study II*: Cox-proportional hazard model adjusted for age, sex and CHD risk factors

Psychological factors	Model a			Model b			Model c		
	HR	CI (95%)	p	HR	CI (95%)	p	HR	CI (95%)	p
Mastery (n=781)	0.62	0.47-0.82	0.001	0.62	0.46-0.85	0.003	0.67	0.46-0.97	0.034
Self esteem (n=777)	0.64	0.48-0.86	0.003	0.64	0.47-0.86	0.004	0.69	0.47-1.00	0.048
Sense of coherence (n=796)	0.70	0.52-0.95	0.023	0.70	0.51-0.96	0.031	0.78	0.55-1.15	0.217
Cynicism (n=800)	1.04	0.76-1.43	0.777	0.96	0.68-1.36	0.851	0.92	0.64-1.31	0.655
Hostile affect (n=796)	1.12	0.84-1.52	0.449	1.11	0.81-1.53	0.516	1.06	0.76-1.48	0.715
Vital exhaustion (n=799)	1.56	1.16-2.08	0.003	1.46	1.07-1.97	0.014	1.34	0.88-2.03	0.169
Hopelessness (n=794)	1.56	1.15-2.11	0.003	1.59	1.16-2.17	0.003	1.48	1.06-2.08	0.023
Depressive symptoms (n=803)	1.58	1.20-2.08	0.001	1.45	1.09-1.92	0.009	1.40	0.85-2.27	0.185
Depressive symptoms* (n=803)	2.47	1.21-5.04	0.001	2.31	1.09-4.91	0.028	-	-	-

Hazard ratio expressed per SD increment except for depressive symptoms, defined as a dichotomy based on 16 or above on CES-D score.

Models adjusted for a) age and sex, b) age, sex, diabetes, BMI, Blood pressure, bloodlipids, smoking, physical inactivity, high alcohol intake, low fruit & vegetable intake, c) as model b plus depressive symptoms (CES-D >= 16).

* Dichotomy.

37. Feasibility of MBSR for Coronary Heart Disease Patients With Depressive Symptoms (*Study III*)

Seventy-nine patients were invited, 24 patients started the MBSR course (30 % of invited), and 16 completed the 8-week intervention. The patients who completed the intervention were generally very satisfied with the MBSR-course and gave the course as a whole the grade 8.3 on a scale from 1 to 10. Interestingly, the most appreciated parts were the weekly meetings (8.1) and the yoga practice (8.0), while written reflections after practice were least appreciated (5.4). Ninety-three % of participants reported that they felt that the course was worth invested time and energy, and 100 % would recommend the course to a friend (Table 4).

Table 4. Results *Study III*: Evaluation of participants' experiences of the 8-week MBSR program assessed immediately after the intervention (n=13).

Items	Mean grades 1-10 (10=excellent)
Overall evaluation of the MBSR course	8.3
Weekly meetings at the hospital	8.1
Body-scan practice	7.4
Sitting meditation	7.4
Walking meditation	5.6
Yoga practice	8.0
Written reflections	5.4
Informal practice in everyday life	6.5
Teacher	9.0
Cours administration	9.1
Will recommend MBSR to a friend with health difficulties	100 %
	79 %
Learned something of lasting value	93 %
Worth the time and energy	

Immediately after the MBSR-course, CES-D scores had decreased by 33 %, and the decrease remained after 12 months. A much smaller and non-significant increase was seen for Mastery immediately after the course. However, Mastery scores had improved after the course and at 12-month follow-up the improvement compared to before MBSR, they were statistically significant compared to before the start (+ 8.7 %) (Table 5 below).

The other measured psychological variables (Mindfulness, Acceptance, Anxiety, Sleep quality and Ladder of Life) showed statistically significant changes in the expected direction, between before and after MBSR (Table 5 below).

Table 5. Results *Study III*: Psychological variables in patients who completed the MBSR program (n = 16)

	1 m	Range	pre-MBSR*	post-MBSR	Pre- vs post change	Pre- vs post p	12 m	Pre- vs 12 m change**	Pre- vs 12 m p
CES-D	19 (7.0)	0-60	20 (8)	13 (8)	- 33 %	0.006	13 (7)	- 33 %	0.005
Mastery	-	7-28	21 (2)	22 (3)	+ 6.3 %	0.110	23 (3)	+ 8.7 %	0.005
FFMQ	-	29-145	85 (9)	94 (12)	+ 11.5 %	0.001	96 (12)	+ 14 %	0.003
AAQ-II	-	7-49	19 (6)	15 (7)	- 20 %	0.002	14 (5)	- 29 %	0.002
GAD-7	-	0-21	7.5 (5)	4.3 (3)	- 43 %	0.004	4.4 (2)	- 41 %	0.005
KSQ	-	0-4	2.9 (1)	3.3 (1)	+ 14 %	0.014	3.3 (1)	+ 14 %	0.033
Ladder of life		0-10	5.6 (1)	6.5 (2)	+ 16 %	0.034	6.5 (2)	+ 16 %	0.038

In the reference group, there were no significant changes in depressive symptoms or Mastery scores, during the 12 months follow-up period (Table 6.).

Table 6. Results *Study III*. Mean scores on the CES-D and Mastery scales in the reference group at 1 and 12 months after the index CAD event in all patients and in the subgroup with CES-D $\geq$ 8 at 1 month.

	1 month	12 months	p
CES-D			
All patients, n = 108	9.0 (7.6)	9.5 (8.6)	0.886
CES-D $\geq$ 8			
at 1 month, n = 56	14 (7.2)	12 (8.1)	0.082
Mastery			
All patients, n=108	23 (3.0)	23 (3.1)	0.144
Mastery (CES-D $\geq$ 8)			
at 1 month, n=56	22 (2.7)	22 (2.9)	0.116

Values are given as mean (SD).

38. Patients Experiences of Mindfulness Practice (*Study IV*)

Twelve diaries were available for analysis, and a total number of 459 quotations were judged to capture key thoughts or concepts in the data. Our analysis revealed the main category: *a journey through chaos and calmness*, which captured participant's experience of challenges and rewards over time. This main category seemed to reflect a journey through both difficulties and positive discoveries and resulting in the harvesting of the fruits of mindfulness practice. Participants described difficulties, both physical and psychological, during the whole course, but as the weeks passed they more frequently described an enhanced ability to concentrate, relax and deal with distractions (Table 7 below).

Table 7. Findings in Study IV:

Main category: A journey through chaos and calmness

Categories	Sub categories (N=459 meaningful units)	Week*		
		1-2	3-6	7-8
Facing the challenges of daily practice	Struggling with doubts and practical obstacles (n=53)			
	Struggling with a distracted and distressed mind (n=92)			
	Struggling with bodily sensations (n=82)			
Harvesting the fruits of daily practice	Being more open to the flow of mental content (n=58)			
	Beginning to sense positive effects (n=153)			
	Experiencing benefits of practice in everyday life (n=21)			

* Bars represents proportions of meaningful units written in the beginning (week 1-2), middle (week 3-6) and the end (week 7-8) of the MBSR course, in the respective sub category.

DISCUSSION

39. Main Findings

STUDY I

Study I showed that the self-report instruments Mastery, Self-esteem, and CES-D seem to be valid ways to assess psychological variables in the context of CHD. When the scales were divided into subscales with only positive and negative items, the subscales followed the same pattern of relationship to other psychological variables, and to biological outcomes, as the original scales. The only exception was the positive items in CES-D, which deviated from the original scale, suggesting that they might weaken the validity of the instrument. However, our results show that the net effect of these four items was very small. Our findings concerning Self-esteem are contrary to those of Martin et al. who showed a solid two-factor structure in Self-esteem [261], and more in line with earlier research from Greenenberg et al. [262]. They showed that the seemingly different factor structure in the Self-esteem scale did not affect their respective relationship to other psychological variables. Our findings of solid validity for the Mastery scale is in line with results published by Eklund et al. [263] who found evidence for validity in the context of mental illness. However, none of these self-report instruments have been validated in a CHD context before. Our overall findings strengthen the usefulness of these instruments in the study of the relationship between psychological variables and health in general, and in CHD in specific.

STUDY II

To our knowledge, *Study II* was the first to show that Mastery and Self-esteem, were independently associated with 8-year risk of CHD incidence, even after adjustment for nine traditional CHD risk factors, including depressive symptoms. These findings are in line with, and extend, an earlier study that linked Mastery to increased risk of cardiovascular mortality [141], and a 5-year follow study up of a Finnish population, which showed that Self-esteem was associated with all-cause mortality [140]. However, in the latter study of Stamatakis et al. the relationship between self-esteem and mortality was lost when adjustments were made for hopelessness, depression, and hostility. Since only a handful of earlier studies have shown a protective effect of psychological resources on CHD incidence, these findings add important knowledge that extend what is known about psychological factors and CHD. These findings strengthen the argument that psychological factors should be looked for, recognized and addressed in both CHD patients and in the general population [264].

The Positive Psychology movement, with its emphasis on strengths, virtues and sustainable well-being, has challenged the research agenda in clinical psychology. The rationale for this artificial divide between “positive” and “negative” is that a focus on positive functions could transform psychology into a truly preventive science [265]. One might argue that our explorations, and critical evaluation, of the impact of psychological resources in CHD, are fully in line with this ambition. Our findings provide a rationale for further exploration of the possibility that a focus on building resources might be a more effective way to prevent the development of disease than to aim at the reduction of stress and distress.

Study I and *II*, demonstrating the validity and usefulness of three self-report instruments, make a small but significant contribution to the longstanding debate over the value of self-report data and provide a rather innovative set of psychobiological evidence for the relevance and accuracy of these instruments.

STUDY III

Study III was envisioned as an attempt to offer the most intense mindfulness-based intervention to a group of patients with high levels of distress, and test the feasibility of implementing MBSR as a complement to conventional cardiac rehabilitation. Our findings showed that only a minority of invited patients were interested and could manage the practical circumstances of attendance. Those who started and completed MBSR (roughly 2/3 of those who started) were very satisfied with the course and held it in high esteem in their evaluations. The withdrawal of eight out of 24 patients from the MBSR group could be viewed as a negative feasibility outcome. However, it also reflects the well-known fact that MBSR can, paradoxically, be stressful and demanding [266], which was something we subsequently showed in illuminating detail in *Study IV*. Our completion rate of 67 % was higher than the MBCT study of depressed CHD patients published by O'Doherty et al. [234], in which only 53 % completed MBCT. Our results are similar to the findings of Zernicke et al. [267] They offered the MBSR-course to irritable bowel syndrome (IBS) patients and reported a completion rate of 66 %. Pbert et al. offered MBSR to asthma patients, and in this study, 85 % completed the intervention [268]. When interpreting these findings, it is important to have in mind that our participants, as well as those in the O'Doherty study, were recruited on the basis of a lack of energy and vitality, which was not the case in the IBS- and asthma studies. Our results showed, rather surprisingly, that the group of patients who decided to participate in MBSR was having significantly higher levels of depressive symptoms, compared to those who declined the invitation. Perhaps the patients who signed up were aware of their difficulties with stress, anxiety and low mood, and thus found the prospect of learning new ways to deal with their suffering appealing.

The significant and sustained reduction in depressive symptoms was not unexpected, since improvements in depressive symptoms, as a result of participation in MBSR, have been shown in systematic reviews of other populations and patients [220,221,222]. Still, these results represent preliminary evidence for a salutary effect of MBSR in this context and the observation that depressive symptoms did not change over 12 months in the reference group strengthens this interpretation.

Our findings in *Study III*, that patient's sense of Mastery seemed to increase gradually over the course of the 12 months that followed participation in MBSR, is notable and should stimulate further study into the important question of how plastic the psychological resources are and thus, if they respond in significant ways to interventions. In *Study III*, we hypothesize that Mastery might be a rather stable trait, and previous theoretical work have characterized it as *learned appraisals* of coping abilities [269]. As such it might require new experiences of life's inevitable hardships, which participants can test their strengthened coping skills against, before their sense of Mastery increase. This interpretation is in line with the proposal of Lindsay and Creswell, cited in chapter 30, that mindful awareness of stressful stimuli could simultaneously buffer against stressful experiences and strengthen the appraisal of coping abilities [238]. It is worth repeating that these findings should be interpreted as hypothesis generating and future studies should replicate them in trials with aims and designs that could generate more conclusive results. It is relevant to ask the critical question if a 2-point increase in Mastery has any clinical consequences. Here it becomes interesting to compare the preliminary findings from *Study III* with the more conclusive results in *Study II*. Our analysis of the 8-year follow-up data on Mastery and CHD risk showed that a 3.4-point increase (1 SD) in Mastery at baseline was associated with a 33 % lowered 8-year risk in CHD incidence. Against this background, a 2-point increase seems to be clinically relevant, and these preliminary findings should be replicated in a larger material with adequate control conditions.

The preliminary results from the 12-month follow up of psychological variables, although only hypothesis generating, does provide encouragement for a continuation of the study of mindfulness and yoga for CHD patients. It is certainly premature to recommend a broad implementation of MBSR as an optional complement to conventional cardiac rehabilitation, from the results of *Study III*. However, parallel to the exploration of possible adaptations of MBSR to the cardiac rehabilitation context, and might be based on trials with various lengths and amounts of daily practice, a large randomized actively controlled effectiveness trial should be carried out. The results from our feasibility trial provide a rationale for such an ambitious and necessary study. In the light of our findings from this feasibility study, it is clear that MBSR has a number of advantages and limitations in comparison with other interventions that have been tried as a treatment for psychological distress in CHD. One main advantage is that MBSR address bio-psycho-social suffering and distress in the broadest possible sense. As such it is especially suitable for the implementation in the medical/somatic context, since patients often have comorbidities, and it provides an opportunity to include a mix of patients.

A second advantage is that MBSR, if its effectiveness will be confirmed future trials, could be more easily integrated into cardiac rehabilitation, than many other psychological treatments, which might require the availability of psychologists or psychiatrists, which seldom are represented in the cardiac rehabilitation team. Although teaching mindfulness requires extensive personal experience of meditation and yoga, and instructors need adequate teacher training [200], professionals already part of the cardiac rehabilitation team, such as cardiac nurses or physical therapists, could train to become teachers. Today, the availability of adequately trained teacher remains a limitation, but it does not have to continue to be so. The implementation and integration of MBIs into health care is a balance act in which the need for more teachers should be weighed against the risks of letting inexperienced professionals teach mindfulness and yoga.

The scalability-advantage of MBIs could also prove to be even more beneficial in areas of the world where the availability of psychologist and psychiatrist are not only scarce on the level of the cardiac rehabilitation unit, but also on a regional and national level. Indeed, recent studies from developing countries have shown that limited interventions provided by local health assistance can be surprisingly effective in reducing depressive symptoms [270]. Mindfulness-based interventions have not yet been explored in this context. However, since CHD continues to rise in developing countries, the cost-effective methods of mindfulness and yoga practice could play an important role.

STUDY IV

Even though the name implies that MBSR offer *stress reduction*, the methods of mindfulness meditation and yoga, is really about the gradual building of the ability to relate skilfully to challenges and hardships in real life. Indeed, the results from *Study IV* showed that the practices in MBSR were experienced as challenging and hard, but also that the application of mindfulness skills to the challenging moments was accompanied by rewarding experiences. This meeting of resistance with presence, openness and acceptance may represent the building of resources in action. Our findings suggest that the dynamic interplay of struggles and rewards, as well as the attempts to deal constructively with it all, may underlie the strengthening of mindfulness skills that theories of mindfulness stipulates [209,211].

The category *facing the challenges of daily practice* was a prominent facet of participant's experience. This aspect of mindfulness practice has not received the same amount of attention in earlier studies of mindfulness. Malpass et al. summarized 14 qualitative studies of mindfulness and reported only one theme that border to a struggle-facet (*facing the difficult*) [271]. Griffith et al. was studying a population similar to our MIMIRA-population and reported almost exclusively positive experiences,

and the only minor negative theme was *struggles with the body scan practice* [270]. Our findings are more in line with Morone et al. who also used content analysis of diaries to study the experience of chronic pain patients participating in MBSR. The reported difficulties in finding time to practice and becoming sleepy while practicing, in addition to more positive themes such as pain reduction, improvement in attention skills and well-being [273].

Our findings in *Study IV* highlight the importance of skilful guidance during the challenging parts (which could indeed be the whole course), of MBSR, since patients might need both motivational and emotional support. Moreover, it is vital to help participants to realize that the challenges are not only workable but also grist for the mill for their development of resilience skills. These findings, based on qualitative data analysed inductively, are in line with previous theories about how the salutary effects of mindfulness training are mediated.

Study IV also show that the study of patients experiences, expressed in diary entries, can answer research questions that are difficult to address with quantitative methods. It is quite amusing to note that a century after the introspective perspectives of William James and Wilhelm Wundt, the fathers of psychology, became discarded as unscientific, we are now living in a time where qualitative studies, and introspective treatment modalities, are now accepted parts of clinical psychology. Furthermore, the study of consciousness is in the process of rising to the status of a real scientific field, with its attributes of conferences and scientific journals [274].

HEALTH BEHAVIOURS AND THE ARTIFICIAL DIVIDE

The four studies in this thesis, with their focus on the measurement and the impact of psychological resources and risk factors, as well as their relative changeability by mindfulness training and yoga, have partly excluded a potentially fruitful area of investigation, namely *health behaviours*. In *Study I* and *II*, smoking, physical activity, and intake of alcohol and fruit and vegetables, were measured, and their effects were adjusted for in the models that investigated independent effects of psychological variables. The relative usefulness of this procedure is discussed in detail in Methodological Considerations (Chapter 40), and land in the conclusion that the research question is the determinant of a wise relationship to these ontological and methodological dilemmas.

These *indirect pathways*, between psychosocial variables and CHD that health behaviours represent, are important targets for further study for numerous reasons. In one fundamental sense; health behaviours *are* psychological factors with its dynamic relationships to both resources and risk factors and the biology of CHD. This basic insight could inform researchers of new possibilities of integrating psychosocial intervention with health behaviour change interventions. Maybe a bridging of this artificial divide, both in clinical practice and in the psyches of our patients, could be a fruitful way forward. Future studies should explore ways to integrate the building of psychological resources with interventions designed for health behaviour change and explore interactive, perhaps even synergistic, effects on well-being and health. The health behaviour of physical activity could be especially fruitful to combine with mindfulness practice, either sequentially or fully intermixed. There are psychological effects of physical exercise, such as enhanced learning, elevated mood, and reductions in anxiety, which could act in synergy with the salutary effects of meditation, and possibly also help participants to deal with the challenging facets described in *Study IV*. Mindful walking is after all an esteemed practice on long silent retreat, so why not investigate mindful running, mindful biking and mindful swimming?

Our findings in *Study III* and *Study IV*, suggests that mindfulness and yoga may be very promising candidates as a central hub for the integration of methods to simultaneously address psychological risk factors and resources, health behaviours and medical treatment. This hypothesis is supported by other areas where mindfulness training has been integrated successfully into the treatment of smoking and substance use disorders [275]. The psychiatrist Judson Brewer has argued that the broad salutary effects of mindfulness might reflect that there are common underlying psychopathologies in depression and substance use [276]. In the light of the theories presented in this thesis, and the proposal of psychobiological tolerance as a bridging principle, it is possible that the Buddha was correct with his insight that there is one unified source of human suffering – attachment.

CONNECTING THE DOTS – A PSYCHOBIOLOGICAL THEORY OF TOLERANCE

As evident from the brief review of mechanisms of action in chapter 26, there are a lot of constructs proposed, and there is a rather large overlap between them. This state of affairs could be viewed as normal for a scientific field that is rather new and currently in a dynamic process of maturation. However, it could also, in the light of the historical context, be viewed as a legacy from the psychological field in which construct proliferation has been a dilemma since the beginning. Either way, future integration of theories, methods, and results from different schools, and from new insights in biology and neuroscience, could represent a major step in a truly maturing direction, in every sense of the word. Perhaps the suggestion of a unifying *psychobiological theory of tolerance* could provide such theoretical scaffolding. Interestingly Nila et al. have investigated how *distress tolerance* is related to resilience and mindfulness in a longitudinal controlled pilot trial of MBSR to 46 healthy volunteers [277]. They found that the 8-week course led to increases in distress tolerance and resilience and that these effects were mediated through changes in mindfulness.

A *psychobiological theory of tolerance* takes a broader stance and would be defined by the multifaceted relational process between an organism and its environment that regulate psychological and physiological systems in ways that are shaped by evolution to promote survival and thriving. The analogue meaning of the term tolerance in immunology is quite illuminating as a metaphor and sheds light over how the Buddhist concept of *selflessness* (or emptiness) could be integrated into this theory of tolerance. Furthermore, there are striking similarities between immunologic- and psychobiological tolerance when things go wrong; when pathology develops and is sustained. For example, *generalized anxiety* disorder could be viewed as an *allergy* of the mind, in which non-harmful stimuli provoke a strong emotional and behavioural reaction characterized by intolerance of uncertainty, experiential avoidance, and activation of stress response pathways. The main prediction from a psychobiological theory of tolerance would thus be that it is the pathological, secondary, psychobiological reactions of *intolerance* of negative emotions, rather than the immediate experience of the emotion itself, that exerts a toxic effect on the body, and over time translates into deleterious health outcome.

This proposal is also supported by the well-studied phenomenon of the U-shaped relationship between stress and negative psychobiological consequences. Mild to moderate levels of stress, coupled with a degree of perceived control is stimulating and healthy [155]. It has also been shown that moderate amounts of cumulative lifetime adversity predict lower level of distress and higher levels of life satisfaction compared to low levels of prior adversity [278]. This suggests that, analogous to the hygiene hypothesis of allergies, that the human psychobiological system actually need a certain amount of adversity and suffering for resilience to develop. A scientific exploration of how *psychobiological tolerance* could be cultivated, strengthened and sustained, could possibly contribute to unifying efforts to improve psychological factors, health behaviours (physical activity, diet, and deleterious habits) and pharmacological treatment of basic physiological risk factors such

as blood pressure and blood lipids, into a coherent whole. Besides inspiring novel and integrative ways to intervene, the coherent story of a unifying theory of psychobiology could also be of educational value in the clinical challenge of reaching out to patients and finding them where they are.

When researchers and clinicians are determined to investigate and implement novel ways to intervene, they traditionally risk an overemphasis on treating away distress addressing psychological risk factors. This kind of *instrumental* ambition, which George Engle might have criticised as the medicalization of patients suffering, could paradoxically represent a blocking to the profound transformation laying at the core of mindfulness and yoga practices. Indeed, at the heart of meditation practice lies a courageous willingness to see, open to and being with things as they are (including the edgy and ugly facets of being a human). Moreover, by increasing the ability to let things be, students in mindfulness can transform the experience of self and life, even if depressive symptoms or anxiety are not entirely treated away. The findings from *Study IV* showed that the most challenging experiences inherent in the practicing of mindfulness skills might be necessary ingredients for learning new and more resilient ways of being. The Vietnamese Zen master Thich Nath Hanh has expressed this principle poetically in his pointing out that we would not get any Lotus flowers without the mud at the bottom of the pond [279].

This discussion takes us to the complex existential facets of an individual's subjective experience. Although the *sense of meaning*, as we saw in chapter 20 and in *Study II*, can be conceptualized, measured, and investigated as a psychological resource, there are unique existential challenges present for every sentient and impermanent being on this planet. Every Homo sapiens has his or her unique way of dealing with the second law of thermodynamics, which stipulates that all of us will eventually face old age, disease, and death [280]. This way of dealing with impermanence might be one of avoidance and intolerance or one of courageousness and tolerance.

40. Methodological Considerations

STUDY I

In *Study I*, we investigated the validity of the self-report instruments Mastery, Self-esteem and CES-D in the context of CHD, with special attention to the use of inverted items. Our evaluation of different facets of validity was based on a “triangulation” process. The reliability of this triangulation depends on knowledge of how the variables have been related to each other in previous studies, and none of our criterion variables could be viewed as a *gold standard* to validate the other scales against. This is in part a limitation of the study but our choice of using biological outcomes as criterion measures could be viewed not only as pragmatic but also innovative. The use of biological and clinical outcome as tools to validate psychological instruments is not seen very often in the literature, and our example in *Study I* could possibly inspire more studies of this kind. Indeed, if we are to further deepen our knowledge and understanding of psychobiological processes and relationships we need to continue to validate our instruments in the particular context we plan to use them.

The vast majority of the results in this thesis (*Study IV* being the exemption) are based on data of psychological variables derived from self-report instruments. The validity of these measurements merits considerations since self-report methods are often criticized for inherent bias from demand characteristics among participants [281]. Although self-report methods have a somewhat bad reputation in this regard, they continue to be widely utilized in all social sciences. According to Haefel et al. the cause is not that scientist are lazy, cheapish and entangled in tradition. It is because they indeed can be as valid a method as any biological or behavioural measures [281]. Haefel et al. address the lack of trust in self-report methods from a philosophy of science perspective and complement this with evidence for the notion that self-report measures are well suited for assessment of a number of theoretical constructs, including cognitive content such as attributions, plans, attitudes, beliefs, emotions, and moods. Also, and even more controversial, they cite evidence that self-report may be a valid indicator of behaviour [281]. It should also be noted that researchers have very few alternatives to self-report instruments when they want to measure broad constructs such as Self-esteem and Mastery since these phenomena are subjective by nature.

With this short resurrection of the scientific status of self-report instruments, the apparent limitations of the methods need to be acknowledged. Respondents may be influenced by a willingness to please the researcher (or him- or herself). Furthermore, they may have difficulties understanding the questions and may also lack the necessary self-awareness and insight to respond to them accurately. Moreover, respondents may fill out questionnaires in a hurry or in a lazy manner that create bias from response errors. Based on what is known about the general validity of self-report instruments [281] we can briefly evaluate the instruments in *Study I-III*, and decide if they are:

1. Measuring a construct with a solid *theoretical background*? (Measure decision and precision depend on well-articulated theories.)
2. Measuring psychological *content* or *processes*? (Content is more reliably reported.)
3. Require high level of insight from respondents? (Sometimes the predictive validity can be high even when respondent's self-insight is not accurate; e.g., perceived stress).
4. *Transparent* in what they measure? (Transparency might drive demand characteristics).

It is beyond the scope of this chapter to scrutinize every individual self-report instrument used in the three quantitative studies, but the following conclusions could be drawn. The psychological resources Mastery, Self-esteem and Sense of Coherence, are all based on a clear theoretical basis, e.g., their hypothesized salutary effects when score are high. They mainly measure psychological *content* and do not require a specifically high amount of insight of psychological processes among respondents. It is quite obvious what they intend to measure which could lead to demand bias.

The same verdict, with the same motivation, will fall over the risk factors (CES-D, Vital Exhaustion, Cynicism, Hostile affect, Hopelessness, and Anxiety) measured in *Study I-III*. When it comes to the secondary outcome measures of Mindfulness (FFMQ) and Acceptance (AAQ-II), it could be argued that they measure more complex psychological process that requires a higher level of self-awareness among respondents. Ironically, and psychometrically troubling, the FFMQ is partly assessing the ability to be self-aware, which might result in that an instrument is measuring different phenomena among participants in the lower- and higher ends of the continuum. Indeed this questionnaire has been criticized for measuring different things in people with and without training in mindfulness meditation [282].

In *Study I* we specifically investigated if the use of inverted items endangers the validity of these instruments in the context of CHD. The relative advantages and disadvantages of using inverted items have been debated for decades in the psychological literature. These questions are also closely related to the question of which psychological constructs should be viewed, and thus measured, as one-dimensional phenomena, a continuum with opposite ends, or if they are multi-dimensional in nature.

It is not very surprising that these questions have been debated since there are at least three possible sources of bias inherent in this procedure. Firstly, the attempt to capture psychological phenomena in a collection of questions requires the use of a language that has to mean the same thing for both researchers and respondents. Another risk, related to both language use and dimensionality, is that the constructs of a scale can create the illusion of a one-dimensional phenomenon, but actually tap into a number of separate psychological processes in respondents. Secondly, data from the instrument, which suggest that the phenomena might be multi-dimensional, could also be the result of systematic response errors. Thirdly, if researchers actually capture the concept in question, with the items of the instrument, there is still the philosophical question if the phenomenon is one- or multiple dimensional in its true nature. This ontological consideration leads to the related question; is it possible to measure a positive phenomenon with negative items accurately, and simply invert the scores when coding the results? All these highly debated questions raise concern if the routine inclusion of inverted items might constitute a validity risk.

STUDY II

Both *Studies I and II*, derive their main results from calculations of Cox Proportional Hazard Ratios of 8-year CHD risk. As can be deduced from the publication dates, *Study II* was performed before *Study I*, and we could base our choice of method on results from the former one. This statistical method provides valuable opportunities to explore associations and inferring potentially causal mechanisms from time-dependent data [283]. The model also allowed us to calculate the hazard ratio (HR) for every standard deviation (SD) of change in scores of the psychological variables, which allowed comparisons between scales.

There are, however, risks of bias inherent in this modelling procedure. In our chosen model, there is a risk that participant's health status at the onset could influence the results. Although the participants were free from CHD diagnoses at baseline, we know that the pathophysiology of CHD is one of slow progress in atherosclerotic burden. Furthermore, both psychological variables and later CHD incidence could be related to health status at the onset. Our adjustment for factors that could be either confounding factors or important effect modifiers (or both, depending on research question), there is a high risk that they could eliminate any relationship between psychological variables and incidence in CHD. These risks of bias would have posed a greater threat to the reliability of our results if our models had revealed no associations between the psychological variables and incidence in CHD, but we still need to be aware of these limitations when we interpret the relative strength of the observed relationships.

The prospective design behind our study of 8-year incidence represents a major strength that also allowed us to infer that there may be a causal link between the psychological resources and risk factors and incidence in CHD. However, as in most prospective studies, the model is based on baseline data of the psychological variables, and we lack insight about how the levels of our psychological variables might have fluctuated during the years leading to a coronary event. A study design with multiple measurements, at various points in time, could add valuable knowledge about the dynamics inherent in these intricate, and potentially reciprocal relationships.

In *Study II*, three Cox proportional hazard models were used, in which we controlled for a) age and sex, b) age, sex and nine well-known CHD risk factors, including the health behaviours of physical activity, diet, alcohol intake and smoking, and c) all the other factors and depressive symptoms. This procedure allowed us to investigate if the psychological resources had an *independent effect*, which most of them indeed had. The third step, with adjustment also for depression, is not seen very often in other studies. It is worthy of note that our results revealed that Mastery and Self-esteem still had significant protective effects while the protective effect of SOC was lost. The advantages and disadvantages with adjustment for possible effect modifiers depend on the research question asked. In *Study II* we were specifically interested in the independent risk contribution of the psychological variables, but if we return to the big picture and consider the whole, and more complex contribution of psychological processes, states, and traits, we might need to think differently.

As we have seen in the introductory chapters about the potential mechanisms that mediate the relationship (social, psychological, central nervous, autonomic, endocrine, hematologic and immunologic), the pathways are very complex and probably bi-directional. If this complexity was not enough, we need to consider that one of the main pathways between a psychological state or trait, and a ruptured atherosclerotic plaque in the coronary arteries, might be through behavioural consequences. If the full impact of a psychological variable was the focus of the investigation, it could be wiser to not control for health behaviours but view them as important mediators.

STUDY III

In *Study III*, we used an open design with a longitudinal observational reference group instead of a traditional control group. The motivation behind this choice was pragmatic and motivated by the time and resource consuming procedure of screening and recruiting patients to the study population. Although the reference population had very similar basic characteristics and was recruited consecutively from the same outpatient clinic, any straightforward comparisons should be avoided. This is mainly motivated by the fact that this group was assessed at 4-6 weeks after their event and then after 12 months, while the MBSR participants provided their base-line data between 1 and 11 months after their event (mode 6 months), and the 12-month follow-up came a year after MBSR completion, not a year after the CHD event. The real value of the reference group was that it showed that depressive symptoms and levels of Mastery did not change during the 12-month period of conventional cardiac rehabilitation. This represents an important reference when interpreting the preliminary evidence for salutary effects among the participants in the MBSR-group. This limitation in study design, and the fact that the group of completers was small, and that primary outcome was feasibility, mean that all observed changes in the psychological variables, seen in *Study III*, should primarily be seen as preliminary and hypothesis generating, and as positive indicators of feasibility and relative safety of the intervention.

The fact that all outcome measures were changing in the expected direction does however lend some support to the hypothesis that MBSR may have salutary effects on psychological variables in CHD patients with depressive symptoms. Furthermore, the limitations associated with the small number of participants and the open design, would have posed a larger problem if the trial had resulted in null- or negative findings.

STUDY IV

Study IV investigated participants experiences of the practices in MBSR with a qualitative content analysis of training logs (diaries). The choice of method was inspired by DeLongis et al. who have argued that diary studies are especially suitable and useful when the focus is on examining change, especially across relatively brief periods of time [284]. The use of data from diaries has methodological advantages and limitations. Compared to the alternative qualitative method of deep interview, using diaries could be less affected by recall bias [285], since participants were instructed to write in proximity to the practice sessions. Furthermore, the continuous writing of entries during the 8-weeks provides a possibility observe changes in content that might not be apparent if participants would be interviewed on one occasion. However, one major limitation of the diary method is that it cannot follow up particular interesting content with probing additional questions. What is written down is what you got.

Lastly, another possible limitation of *Study IV*, was that the number of diaries available for analysis ($n=12$), was not motivated by methodological reasoning, or from a consecutive analysis of saturation in content from the previous diaries. Instead, it was a consequence of the fact that 16 participants completed the MBSR course and 12 of them provided notebooks adequately filled with diary entries. However, in our analytic process, we could see that no new codes were added to the emergent subcategories after the first 10 diaries.

41. Conclusions

- + The use of inverted items in the self-report instruments Mastery, Self-esteem, and CES-D (depressive symptoms), does not seem to represent a validity risk when the questionnaires are used in the context of CHD risk.
- + The psychological resources Mastery, Self-esteem, and Sense of Coherence, were associated with a decreased eight-year incidence in CHD, while the psychological risk factors depressive symptoms (CED-D), Vital exhaustion and Hopelessness were associated with increased risk. The protective effect of Self-esteem and Mastery, as well as the increased risk from Hopelessness, remained after adjustment for depressive symptoms.
- + Mindfulness-Based Stress Reduction seemed to be a feasible and acceptable intervention for CHD patients with depressive symptoms after a recent coronary event. Analyses of changes in psychological variables over time showed positive effects on Mastery, depressive symptoms, mindfulness, anxiety, sleep quality, and quality of life. These findings could be interpreted as preliminary evidence that MBSR might be beneficial as a complement to cardiac rehabilitation.
- + Patients with CHD and depressive symptoms experienced the practices of mindfulness meditation and yoga as simultaneously challenging and rewarding during the 8-week MBSR course. These findings highlight the importance of realistic expectations, motivational support and skilful guidance during the journey through MBSR.

42. Clinical Implications

The results in the four studies included in this thesis could have the following clinical implications:

- + The self-report instruments Mastery, Self-esteem and CES-D (depressive symptoms), are valid instruments for the assessment of psychological resources and risk factors in the context of CHD risk. As such, they could be useful in the screening of patients, and healthy people with other risk factors. The instruments may also be particularly suited for the evaluation of psychosocial interventions in cardiovascular medicine.
- + Psychological risk factors and resources, such as patient's sense of Mastery and Self-esteem, are important predictive factors for future cardiovascular health. Our results highlight that patient's psychological resources should be recognized and addressed in the clinical practice of cardiology.
- + It is premature to recommend that Mindfulness-Based Stress Reduction should be broadly implemented as a complement to conventional cardiac rehabilitation. The results from our feasibility trial do, however, provide support for continuing exploration of the benefits of mindfulness and yoga practices for CHD patients. Future studies should investigate their effectiveness and how these practices could be further adapted to suit the need of CHD patients.
- + Cardiac rehabilitation units could investigate existing interest and experience of mindfulness and yoga among the ordinary staff, and management should provide opportunities for mindfulness teacher training. The training of regular staff could be the most sustainable way for mindfulness training to gradually make the transition from experimental complement into a fully integrated and evidence-based part of the rehabilitation process.

43. Future Research

Based on the results of the four studies in this thesis the following ideas for future studies could be advocated:

- + Although Mastery, Self-esteem, and CES-D seem to be valid self-report instruments, it should be noted that the theoretical basis was elaborated four decades ago. Future studies should critically investigate the theoretical constructs in relationship to modern conceptualizations of resilience, coping, and psychological flexibility. These kinds of studies could further strengthen their usefulness and possibly also sharpen their validity as measurement tools.
- + The exploration of psychological resources and risk factors and their impact on CHD risk is still in an immature phase with mixed results and large knowledge gaps. Future studies should replicate key findings and investigate a broader panel of psychological variables, including modern conceptualizations of the basis for resilience and psychopathology.
- + The focus on the building of psychological resources could be a more effective way to prevent psychosocial distress and suffering, than the aim of reducing psychopathology. Future studies should investigate innovative ways to strengthen psychological functions, such as self-regulation skills, to explore if practices that effectively build resources could be developed. Such practices could be of great value in both primary and secondary preventive effort, especially when patients suffering lies just under the level when it could be labelled as a disorder.
- + The confirmed relationship between psychological resources and risk factors and CHD, is likely to be mediated by both *direct effects* (psychobiological pathways) and *indirect effects* (health behaviours). Both are equally important, and both provide opportunities and limitations for the successful rehabilitation of CHD patients. Future studies should further investigate how psychological variables and health behaviour interact in the progression or slowing down of disease development.
- + The overall findings in this thesis provide a rational, and encouragement, for further exploration of the impact of psychological variables in other chronic diseases.
- + The possible role of mindfulness and yoga in cardiac rehabilitation should be further investigated in both effectiveness and mechanistic studies. The time is ripe for a large controlled randomized trial with MBSR vs. another evidence-based psychological treatment or active control. However, it is far from clear today that the format of MBSR represents the optimal way to integrate mindfulness training into cardiac rehabilitation. Future studies should explore alternative ways to integrate these practices into exercise-based cardiac rehabilitation, including intensive retreats, yearlong socially supporting variants and brief self-help practices that could be fully integrated into aerobic exercise. Future studies should also explore which adaptations would benefit the CHD population.
- + Qualitative studies (e.g., diary content analyses) could provide valuable insights about patient's motivation or lack of motivation. Future studies should investigate the immediate experience of participants that decide to withdraw from MBIs, and perhaps this study design could also be utilised to generate knowledge about why a significant proportion of patients fail to change their health behaviour after a coronary event.

CONCLUDING REMARKS

Psychological resources and risk factors are important and under-recognized determinants of CHD. A large number of studies have confirmed this relationship, but there are still significant gaps in our understanding of how psychological well-being or distress translates into vulnerable atheroma in the vascular tree and vice versa. A smaller number of studies have explored ways to intervene and treat psychological distress among CHD patients, but the results have been mixed and sometimes conflicting, and there is a great need for novel methods and further refinement of established methods to treat psychological distress.

Voices in clinical psychology are advocating a focus on positive functioning as a potentially more effective way to prevent distress and illness. Mindfulness and yoga, millennia-old but novel in the context of cardiovascular medicine, are ways of relating to life's hardships that have shown promising results in other contexts during the last two decades. At the heart of these practices lies a cultivation of an enduring and flexible resourcefulness. It is premature to recommend a broad implementation of these interventions in cardiac rehabilitation, but preliminary findings encourage further scientific exploration.

AFTERWORD

A wise movement forward within the field of behavioural cardiology will need to walk a *middle way* between hype and hopelessness over psychological treatments; between thinking in traditional circuits and betting on the exploration of novel methods; between construct proliferation and a simplifying unification, and between the use of cutting-edge technology and conventional methods.

Forty years after Engel proposed the bio-psycho-social argument, we live in an age where medical science is preoccupied with MRI-machines, transcranial magnetic stimulation, robot surgery, genome editing and a growing list of ways to modify the nervous systems with psychopharmacologic agents. This is exciting, and many future patients will benefit from this dramatic increase in advanced technology. However, the basic truth that we are bio-psycho-social mammals, with minds and bodies that have been shaped by evolutionary pressures over long stretches of time, remind us that our horizon of opportunities is broader than most of us think.

Perhaps we need to realize that some human problems require radical simplifications rather than more advanced treatments. This could indeed be the case for psychological resources and risk factors and their reciprocal relationship to CHD.

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Appendix A – Items in the three instruments evaluated in *Study I*

The Mastery Scale (Pearlin & Schooler)

How strongly do you agree or disagree that:

Disagree completely, Disagree to some extent, Agree to some extent, Agree completely

- There is really no way I can solve some of the problems I have. (1)
Sometimes I feel that I'm being pushed around in life. (2)
I have little control over the things that happen to me. (3)
I can do just about anything I really set my mind to do. (4)
I often feel helpless in dealing with the problems in life. (5)
What happens to me in the future mostly depends on me. (6)
There is little I can do to change many of the important things in my life. (7)

The Self-esteem Scale (Rosenberg)

How strongly do you agree or disagree that:

Disagree completely, Disagree to some extent, Agree to some extent, Agree completely

- I feel that I am a person of worth, at least on an equal plane with others. (1)
I feel that I have a number of good qualities. (2)
All in all, I am inclined to feel that I'm a failure. (3)
I am able to do things as well as most other people. (4)
I feel I do not have much to be proud of. (5)
I take a positive attitude toward myself. (6)
On the whole I am satisfied with myself. (7)
I certainly feel useless at times. (8)
I wish I could have more respect for myself. (9)
At times, I think that I am no good at all. (10)

The Centre for Epidemiologic Studies Depression Scale (CES-D) (Radloff)

How often have you felt this way during the last week?

Less than 1 day, 1-2 days, 3-4 days, 5-7 days

- Things that usually don't bother me bothered me. (1)
I did not feel like eating; my appetite was poor. (2)
I felt that I could not shake of the blues, even with help from family and friends. (3)
I felt that I was just as good as other people. (4)
I had trouble keeping my mind on what I was doing. (5)
I felt depressed. (6)
I felt that everything I did was an effort. (7)
I felt hopeful about the future. (8)
I thought my life had been a failure. (9)
I felt fearful. (10)
My sleep was restless. (11)
I was happy. (12)
I talked less than usual. (13)
I felt lonely. (14)
People were unfriendly. (15)
I enjoyed life. (16)
I had crying spells. (17)
I felt sad. (18)
I felt that people disliked me. (19)
I could not get "going". (20)

Appendix B – A four-stage-model of depression

STAGE	DEFINITION	FOCUS OF INTERVENTION	PLATFORM OF CARE	INTERVENTIONS
Wellness	Absence of any sustained, distressing, emotional experiences	Promotion and primary prevention	Community	Promoting nurturing environments for children and adolescents, life skills on promoting mental health, addressing social determinants such as interpersonal violence, etc.
Distress	Mild to moderate distressing emotional experiences, of relatively short duration	Indicated prevention	Community, routine health care*, social welfare	Self-care and low-intensity support through digital or peer interventions
Disorder	Severely distressing experiences, lasting at least two to four weeks, with impairment of social functioning	Treatment to remission and recovery	Routine health care	Brief psychological treatments, antidepressant medication, or a combination of both, in a stepped care approach
Recurrent or Refractory	Unresponsive or relapsing depressive episodes	Relapse prevention and/or stabilization	Mental health care	Intensive psychosocial interventions, augmented pharmacotherapy, electroconvulsive therapy

**Routine health care refers to any health care platform, other than mental health care, where depression is frequent and includes primary, maternal, and chronic disease care.*

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Appendix C - Detailed description of the content of MBSR

Session 1

This session includes a review of the intervention and the establishment of a learning contract with the patients. The theoretical underpinnings of mind-body medicine and the application of self-regulatory skills as related to the patient's referring diagnosis are also established. The patient is experientially introduced to mindful eating, mindful breathing and the body scan. Homework is assigned using the first guided CD (body scan meditation) as a means of beginning to learn to utilize these coping skills in everyday situations.

Session 2

This session includes one hour of experiential training and skill development in MBSR, one hour of focused interactive discussion and dialogue concerning the role of perception, conditioning, and other mental factors in the appraisal assessment of stress, as well as the pivotal role of self-responsibility in the positive development of short and long-term change in health and health enhancing behaviours. Daily homework is assigned with an emphasis on the regular daily practice of the body scan for a second week, plus introduction of short periods of sitting meditation, as well as the application of MBSR skills in the everyday life of the patient.

Session 3

Primarily experiential in nature, this session emphasizes the development of mindful hatha yoga to complement the self-regulatory skills learned during the first two sessions. The patient now practices three distinct yet inter-related formal MBSR methods (body scan, sitting meditation and yoga) for approximately two hours. This is followed by a discussion about the current difficulty and success he/she may be experiencing in learning and applying MBSR in everyday life, as well as suggested strategies for enhancing the transfer of such skills in a variety of real-life stressful situations.

Session 4

During this session, participants engage in a combination of the three major formal mindfulness meditation practices that have also been practiced at home during the preceding weeks. The central theme of the class is oriented around the use of MBSR skills as a mean of reducing the negative effects of stress reactivity as well as the development of more effective ways of responding positively and pro-actively to stressful situations and experiences. The physiological and psychological bases of stress reactivity are reviewed and in-depth discussion is directed toward the use of MBSR skills as a way of eliminating or reducing the negative effects of stress reactivity. Daily practice of these methods is assigned to the patient for homework.

Session 5

This session marks the halfway point in the course. It emphasizes the capacity of the patient to adapt more rapidly and effectively to everyday challenges and stressors. Experiential practices of MBSR skills continue with an emphasis on developing both problem-focused and emotion-focused coping strategies. A central element of the session is oriented around the patient's capacity to recover more rapidly from stressful encounters when they occur. Strategies continue to be developed with emphasis on the patient's growing capacity to attend more precisely to a variety of physical and mental precepts and to use this awareness as a way of deliberately interrupting and intervening in previously conditioned, habitual behaviours and choosing more effective responses. Daily practice of MBSR methods is assigned for homework, with an emphasis on the observation and application of these skills in the patient's daily life.

Session 6

Experiential training in MBSR continues, with an emphasis on the patient's growing capacity to cope more effectively with stress. Discussion is oriented around the continued development of "transformational coping strategies", attitudes and behaviours that enhance the psychological characteristic known as "stress hardiness". Theory is linked directly to the MBSR methods and skills being practiced, grounded in the actual life experience of the patient. The emphasis continues to be on the broadening of the patient's inner resources for developing heal-enhancing attitudes and behaviours and the practical application of such competencies given his/her particular life situation and medical condition. Daily practice of MBSR methods is again assigned for homework with an emphasis on the observation and application of these skills in the patient's daily life.

Session 7

This session emphasizes both the deepening of the various formal mindfulness practices, as well as the continued development of a more flexible and refined capacity to utilize mindfulness in a wide range of everyday situation. The intensive nature of this session is intended to assist the patient in firmly en effectively establishing the use of MBSR skill across multiple situations in the lives while simultaneously preparing them to utilize these methods far beyond the conclusion of the intervention. This session, called “all day intensive” is seven hours long. It is attended by passed graduates of the program, as well as program participants.

Session 8

Experiential training in MBSR skills continues. The patient engages in an in-depth exploration of stress as it presents within the domain of communications. The focus of this strategy-building session revolves around the application of previously learned MBSR skills and methods in the area of communications. A variety of communications styles including passive, assertive, and aggressive behaviour patterns are examined both didactically and experientially, and strategies for more effective interpersonal communication are developed. MBSR-based homework is assigned and as a way of preparing for the conclusion of the program; the patient is asked to exercise greater personal latitude in the choice of formal methods to be practiced during the week between this session and the final one.

Session 9

Experiential practice of the MBSR method continues and the patient I given ample opportunity to inquire and clarify with the instructor any lingering questions about the various practices and their applications in everyday life. A review of the program is included with an emphasis on daily strategies for maintaining and deepening the skills developed during the course of the program.

From: Saki F Santorelli Ed.D. *Describing MBSR for HMO's and the medical record, from “Mindfulness Based Stress Reduction (MBSR) Professional Training Resource Manual” (2009)*. Published with permission from the author.

Studies

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