From Department of Clinical Neuroscience
Karolinska Institutet, Stockholm, Sweden

MIND AND BODY EXERCISES – ASSOCIATIONS WITH MENTAL HEALTH, ANTIDEPRESSANT MEDICATION, AUTONOMIC FUNCTIONING AND INFLAMMATORY BIOMARKERS

Lina Rådmark

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Mind and Body Exercises – Associations with Mental Health, Antidepressant Medication, Autonomic Functioning and Inflammatory Biomarkers.

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Lina Rådmark

Principal Supervisor:
Walter Osika, MD, PhD.,
Associate Professor
Karolinska Institutet
Department of Clinical Neuroscience
Centre for Psychiatry Research, CPF

Co-supervisor(s):
Eva Bojner-Horwitz, PhD.,
Professor
Royal College of Music in Stockholm
Department of Music, Pedagogy and Society,

Linda Magnusson Hanson, PhD.,
Associate Professor
Stockholm University
Department of Psychology
Stress Research Institute

Scott M Montgomery, PhD.,
Professor
Örebro University
School of Medical Sciences
Clinical Epidemiology

Opponent:
Marie Åsberg, MD, PhD.,
Professor em
Karolinska Institutet
Department of Clinical Sciences,
Danderyd Hospital

Examination Board:
Miek Jong, PhD.,
Professor
UiT The Arctic University of Norway
The National Research Center in Complementary and Alternative Medicine

Anne H Berman, PhD.,
Associate Professor
Uppsala University
Department of Psychology
Clinical Psychology

Irene Jensen, PhD.,
Professor
Karolinska Institutet
Institute of Environmental Medicine
Division of Intervention and Implementation Research in Worker Health

To my children, Noah, Märta and Nisse, with love.

POPULAR SCIENCE SUMMARY OF THE THESIS

Stress, depression and stress-related mental illness are common disorders both in Sweden and globally. Those who are inflicted often turn to both conventional care and complementary methods for counseling and treatment. An example of complementary methods is mind and body exercises (MBE), such as mindfulness-based interventions (MBIs).

Knowledge regarding if, how and when to use MBE, and combinations of MBE and conventional care is largely lacking, which risks to impair the tailoring of best treatment strategies. More knowledge about potential benefits and risks of using complementary treatment methods and combinations of these with conventional care is thus warranted among healthcare professionals, patients, decision-makers and the general public.

The overall purpose of this dissertation was therefore to map the use of MBE, and to study the relationship between MBE and different measures of health, and the use of different medications for depression, anxiety, insomnia and pain. In order to be able to develop evidence-based recommendations and treatment strategies, the purpose was furthermore to investigate whether there are any robust effects of MBIs on biomarkers for stress and depression.

The studies showed that among those who practice some form of MBE, the use of e.g. antidepressant medication was three times higher than amongst those who never practice these methods. So, is the conclusion from these studies that is it harmful to meditate, or to practice any of the other MBE?

It did not turn out to be that simple; when individuals were followed over time, those with mild symptoms to a greater extent seem to practice MBE only, while those with more severe symptoms more often also use medication, in addition to MBE.

Furthermore, the possible effects of MBIs on various biological measures that can be linked to stress and depression were investigated. A meta-analysis (that means an evaluation of studies that examined the effects of MBIs) was performed. In addition, a randomized controlled study was performed, in which expectant women were allotted to either participation in an MBI or to a commonly used childbirth education program. None of these studies showed any significant effects of MBIs on biological markers, when compared to active control groups.

In order to be able to provide any evidence-based advice regarding the benefits and possible risks of MBE, more thorough studies are needed that examine both whether and how MBE works, if there are any specific beneficial or harmful combinations of MBE and e.g. medications, to whom MBE can be recommended, and whether anyone should be advised to refrain from practicing MBE.

ABSTRACT

Stress, depression and stress-related mental ill-health are common in societies all over the world, and people tend to use both conventional care within the health care system and complementary treatment methods to handle the related symptoms. Still, there is sparse information on whether, how and when to combine these different treatment modalities, in spite of their relatively widespread use. There is thus a need for increased knowledge on complementary treatment methods among conventional health care professionals, patients, policy- and decision makers, and the general public. An example of complementary methods is so called mind and body exercises (MBE), which include e.g. mindfulness based interventions (MBIs).

Aims: The overall aim of this thesis was to map the use of MBE and its associations with health and markers of disease, i.e. prescriptions of psychotropics, and to study if there are any robust effects of MBIs on biomarkers of stress. The findings were thus aimed to enable evidence-based recommendations and personalized treatment strategies. The specific aims were: To identify differential associations regarding gender, age, socioeconomic status, health behaviors, perceived stress, self-rated health, and the purchase of prescribed drugs among people who practice MBE extensively, compared to people who do not practice MBE (study I); To further investigate the temporal relationship between MBE, depressive symptoms, purchase of antidepressant drugs and physical exercise, based on the cross-sectional findings in study I (study II); To evaluate existing data on the effect of standardized mindfulness based interventions on inflammatory biomarkers and autonomic nervous system functioning (assessed by measurements of heart rate variability, HRV), through a systematic review and meta-analysis (study III); To investigate the effects of a Mindfulness Based Childbirth and Parenting intervention on HRV and serum inflammatory marker levels among pregnant women, through an RCT study with an active control group comparison (study IV).

Methods: Studies I and II were based on responses from the Swedish Longitudinal Occupational Survey of Health (SLOSH). Measures regarding MBE practice, health behaviors, perceived stress, self-rated health and illnesses were drawn from the SLOSH questionnaire, while data on antidepressant drug purchase for all respondents was obtained from the Swedish Prescribed Drug Register. In study III, a literature search was conducted in collaboration with two experienced university librarians. Literature screening and data extraction were performed independently by two researchers. The methodological quality of included studies was assessed independently by two researchers using the Cochrane Collaboration's tool for assessing risk of bias. In study IV, first time pregnant women at risk of perinatal depression were randomized to MBCP or an active control treatment. At baseline and post-intervention, participants filled out questionnaires and measures on HRV and inflammatory biomarkers were collected.

Results: MBE practice was found to have significant cross-sectional associations with high levels of depressive symptoms and prescribed antidepressant purchases (study I). The temporal investigations of these relationships revealed a more complex picture, where MBE

practice itself was not associated with either subsequent antidepressant medication or with subsequent depressive symptoms (study II). No significant effect of standardized MBIs on inflammatory biomarkers or HRV, when compared to active controls, treatment as usual or wait-list controls, was found – neither in the meta-analysis (study III) nor in the randomized controlled study (study IV).

Conclusions: The findings from study I and II demonstrate the use MBE among the general population as well as in clinical populations like patients suffering from mental ill-health. In order to gain a deeper understanding of the temporality of these correlations, and to delineate possible beneficial or harmful combinations of psychotropics, MBE and other treatment strategies, further research is needed. The findings from study III and IV highlight the necessity of larger, more rigorously conducted RCTs with standardized MBIs being compared to various forms of active controls, also including more long-term follow-ups, in order to provide evidence-based recommendations, both for self-help use and clinical practices.

LIST OF SCIENTIFIC PAPERS

I. Radmark, L., Hanson, L.L.M., Bojner Horwitz, E., Osika, W. (2017). Prevalence of Mind and Body Exercises (MBE) in Relation to Demographics, Self-Rated Health, and Purchases of Prescribed Psychotropic Drugs and Analgesics. Plos One. doi: 10.1371/journal.pone.0184635

II. Radmark, L., Magnusson Hanson, L.L., Montgomery, S., Bojner Horwitz, E., Osika, W. (2020). Mind and Body Exercises (MBE), Prescribed Antidepressant Medication, Physical Exercise and Depressive Symptoms – A Longitudinal Study. Journal of Affective Disorders. doi: 10.1016/j.jad.2020.01.012

III. Radmark, L., Sidorchuk, A., Osika, W., Niemi, M. (2019). A Systematic Review and Meta-Analysis of the Impact of Mindfulness Based Interventions on Heart Rate Variability and Inflammatory Markers. Journal of Clinical Medicine. doi: 10.3390/jcm8101638

IV. Radmark, L., Osika, W., Benka Wallén, M., Nissen, E., Branstrom, R., Gardner, R., Fransson, E., Karlsson, H., Niemi, M. (Manuscript). Autonomic regulation and biomarkers in pregnant women participating in a randomized controlled study of Mindfulness Based Childbirth and Parenting.

CONTENTS

LIST OF ABBREVIATIONS

ATC	Anatomical Therapeutical Classification
EPDS	Edinburgh Postnatal Depression Scale
ES	Effect Size
FFMQ	Five Facets of Mindfulness Questionnaire
HF	High Frequency
HPA	Hypothalamic Pituitary Adrenal
HRV	Heart Rate Variability
LF	Low Frequency
LF/HF	Low Frequency/High Frequency
LLOQ	Lower Level of Quantification
MBE	Mind and Body Exercises
MBI	Mindfulness Based Interventions
MBCT	Mindfulness Based Cognitive Therapy
MBCP	Mindfulness Based Childbirth and Parenting
MBSR	Mindfulness Based Stress Reduction
PCC	Patient-Centered Care
PND	Perinatal Depression
PSOM	Positive States of Mind
PSS	Perceived Stress Scale
SDNN	Standard Deviation of Normal-to-Normal intervals
SEM	Structural Equation Modeling
SLOSH	Swedish Longitudinal Occupational Survey of Health
SNRI	Selective Serotonin Reuptake Inhibitors
SSRI	Serotonin Noradrenaline Reuptake Inhibitors
TCA	Tricyclic Antidepressants
WHO	World Health Organization

1 PREFACE

When I started studying pharmacy at Uppsala University, I was driven by an interest in health and how we can affect our well-being by using not only medical drugs but also herbal drugs and chemical substances of natural origin. Under the supervision of Associate Professor Premila Perera, I got the opportunity to conduct a SIDA-financed Minor Field Study in Chiang Mai in northern Thailand, where we studied the protective effects of an extract of Plantago major for developing peptic ulcers. The research project as such was interesting, but the most profound insights I gained through my stay in Thailand concerned the realization of how meditation and yoga were being used by many as a form of health promotion. My interest in health expanded and came to include also the use of mind body exercises and other forms of complementary methods. Also, I became increasingly interested in how and why people use these methods all over the world. A couple of years later, even that time under the supervision of Associate Professor Premila Perera, I was fortunate to have the chance of travelling to Sri Lanka to conduct my Master's thesis project. The aim was to investigate a treatment method used in Ayurvedic medicine (the traditional system of medicine in India and Sri Lanka) for the treatment of Rheumatoid arthritis. The time in Sri Lanka was a true eye-opener and it was now I really started to reflect upon the big gap that exists between what we call complementary treatments (e.g. the treatment methods that originate from traditional systems of medicine, such as Ayurveda) and conventional medicine in the West. Even though people tend to use these different ways of managing ill-health in combination, the knowledge about complementary methods among conventional health care professionals is sparse. In addition, the attitude towards conventional medicine among complementary and alternative practitioners is sometimes characterized by skepticism. Meanwhile, patients who would wish for an improved communication between these two worlds of practice, are left hanging in-between. Therefore, my wish to contribute to building bridges between these two worlds drew me further into an academic path. In 2013, my friend and fellow pharmacist, PhD Johanna Hök Nordberg, introduced me to Associate Professor Walter Osika. Under his supervision, I began working on the research plan which received funding from the Ekhaga foundation in 2014, and this thesis is the result of that work.

2 INTRODUCTION

This thesis examines the relationships between participation in mind and body exercises (MBE) on the one hand and the use of antidepressant medication, self-reported stress, mental ill-health, autonomic functioning and inflammatory biomarkers on the other.

Stress and stress-related mental ill-health as well as depression, is common in societies all over the world (Q. Liu et al., 2020; Saxena & Setoya, 2014; World Health Organization, 2017), and people tend to use both conventional care within the health care system and complementary treatment methods (e.g. MBE), to handle the related symptoms (Bystritsky et al., 2012; de Jonge et al., 2018; Maria Wemrell, Olsson, & Landgren, 2020). Still, there is sparse information on whether, how and when to combine these different treatment modalities and there is a need for increased knowledge on complementary treatment methods among conventional health care professionals (Bjerså, Stener Victorin, & Fagevik Olsén, 2012; Jong, Lundqvist, & Jong, 2015).

2.1 STRESS AND STRESS-RELATED MENTAL ILL-HEALTH

'Stress' is a broad concept and lacks a universally accepted definition, and the concept of stress has been debated and the need for a common definition and common models among researchers has been highlighted , ever since its first use in biomedical research (Koolhaas et al., 2011).

Current research on stress encompasses different aspects such as: 1) *environmental*, with focus on the assessment of stressors (World Health Organization, 2011); 2) *psychological*, with focus on the assessment of a person's subjective evaluation of his/her abilities to cope with the demands posed by specific events (Ursin & Eriksen, 2004, 2010) and/or the measurement of the person's individual affective response to the demands (Jamieson, Hangen, Lee, & Yeager, 2018; Kirschbaum, Pirke, & Hellhammer, 1993); and 3) *biological*, with focus on measuring the activation of specific physiological systems that are involved in the stress response (Arnsten, 2009; Bruce S. McEwen, 1998, 2007).

Furthermore, stress can be defined either as 1) *acute*, e.g. in response to environmental noise, acute threat to life or other traumatic events (Shalev, 2002); or 2) *chronic*, e.g. work-related stress (Chandola, Brunner, & Marmot, 2006; Karasek, Baker, Marxer, Ahlbom, & Theorell, 1981) and/or absence of social support (Brosschot, Verkuil, & Thayer, 2018; Sheldon Cohen & Wills, 1985), which is intertwined with concepts and diagnoses such as clinical burnout, mental fatigue, sleep deprivation and mental ill-health (Hammen, 2005; Lazarus, 1984; R. T. Liu & Alloy, 2010; Währborg, 2010).

As a result of the different aspects of stress, a number of instruments/questionnaires that are proposed to measure self-reported stress have been developed. Some focus more on the environmental aspects (e.g. 'Job Content Questionnaire', 'Survey of Recent Life Experiences') some on the psychological aspects (e.g. 'Perceived Stress Scale', 'Brief Stress and Coping Inventory') and some on the biological aspects (e.g. 'Profile of Mood States' or

'Impact of Event Scale'). These various instruments are used, for example, in epidemiological research (Kopp et al., 2010).

However, despite the various definitions, there are strong accumulated evidence that stress – acute as well as chronic – has a negative impact on both physical and mental health (R. T. Liu & Alloy, 2010; B. S. McEwen, 2008) and the World Health Organization (WHO) states that high levels of stress and information overload are increasingly contributing to the global burden of disease (Saxena & Setoya, 2014). The relations between stress and mental ill-health in general and depression in particular are well researched and have been confirmed in numerous studies (Hammen, 2005; Kessler, 1997; Paykel, 2003). However, the unidirectional model of the stress-depression association has been found to be too simplistic, and research focus is increasingly turning toward complex models. These models address thus the effects of various contextual factors, specific stressor characteristics, childhood and lifetime stress exposure as well as the changing and dynamic relationship between stress and depression (Hammen, 2005; R. T. Liu & Alloy, 2010).

2.1.1 Burnout and exhaustion syndrome

The concept of 'burnout', first described in the 1970s (Freudenberger, 1974; Maslach, 1976) is commonly regarded as a job-induced syndrome characterized by emotional exhaustion, depersonalization and a lack of personal achievement as a response to prolonged stress. Currently burnout symptoms are assessed with questionnaires such as the Maslach Burnout Inventory (Maslach & Jackson, 1981; Maslach, Jackson, & Leiter, 1996). Despite some dissimilarities between different conceptualizations, emotional exhaustion has been suggested to be a core component of burnout (Maslach & Leiter, 2016). However, WHO has not classified burnout as e.g. a mental disorder, but as a 'state of vital exhaustion' (Z73.0) (World Health Organization, 2010), and WHO states that burnout refers exclusively to phenomena in occupational contexts and should not be used to describe symptoms related to other areas of life (World Health Organization, 2019). Also, the Diagnostic and Statistical Manual of Mental Disorders 5th edition (American Psychiatric Association, 2013) does not include burnout.

In 2003 the concept 'exhaustion syndrome' was described in a publication from the National Board of Health and Welfare in Sweden (National Board of Health and Welfare, 2003). The exhaustion syndrome was there described as being caused by prolonged stress without sufficient restoration and manifested in the form of severe fatigue, cognitive and emotional symptoms as well as somatic complaints (Golkar et al., 2014; Grossi, Perski, Osika, & Savic, 2015; National Board of Health and Welfare, 2003; Savic, Perski, & Osika, 2018; Währborg, 2010).

Sweden is the only country where exhaustion syndrome is classified as a formal ICD-10 diagnosis (F43.8A), and this classification has economic and health care implications.

Both burnout and exhaustion syndrome have been extensively researched in the last decades. Still, there are major concerns regarding e.g. the validity of assessment and conceptual

models (Bianchi, Schonfeld, & Laurent, 2019). Some researchers have had a disagreement on whether burnout, exhaustion syndrome and depression are different constructs or not, and the burnout-depression overlap is still a topic for discussion among researchers in the field (Bianchi et al., 2019; Koutsimani, Montgomery, & Georganta, 2019; Maslach & Leiter, 2016).

2.2 DEPRESSION

Depression – including major depressive disorder and dysthymia – is the most common mental disorder worldwide. It is estimated that more than 300 million people suffer from depression at any time point, being equivalent to 4.4% of the world´s population (Ferrari et al., 2013; Q. Liu et al., 2020; World Health Organization, 2017). Depression is often a very disabling condition that can affect both mental and physical health, leading to substantial societal costs, for example in the form of sickness absence and prescribed medication costs in industrialized countries (Greenberg, Fournier, Sisitsky, Pike, & Kessler, 2015; World Health Organization, 2017), including Sweden (Försäkringskassan, 2014, 2016, 2020; OECD, 2013).

Common symptoms of depressive disorders include depressed mood, loss of interest or pleasure, decreased energy, feelings of guilt or low self-worth, disturbed sleep or appetite, and poor concentration (World Health Organization, 2017). Across the lifespan, the risk of depression is 15-18% and it is almost twice as common among women as men (Malhi & Mann, 2018). Depression relapse is common, where 50% of patients experience a relapse within two years after their first episode (Mueller et al., 1999). Even though the complex pathogenesis of depression is still poorly understood, it is known that both biological, psychological and cultural factors play a role (Malhi & Mann, 2018; Ménard, Hodes, & Russo, 2016).

The two main diagnostic systems in use world-wide – DSM (American Psychiatric Association, 2013) and ICD (World Health Organization, 2010) – outline similar criterion (that is, the number and duration of key symptoms) to diagnose depression. Other tools commonly used to diagnose depression and/or screen for symptoms include validated clinician-based or self-report depression symptom scales/questionnaires, such as the Hamilton Rating Scale for Depression (HAM-D), the Beck Depression Inventory (BDI), the Center for Epidemiological Studies Depression Scale (CES-D), the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Hopkins Symptom Checklist Depression Scale (HSCL-D) (SBU, 2004).

In the treatment of patients with depression, the primary aim is to achieve complete remission of depressive symptoms. Patients can be treated with pharmacotherapy, psychological therapy (such as Cognitive Behavioral Therapy, CBT), electroconvulsive therapy (ECT), or combinations of these methods. Furthermore, depression management often includes the promotion of healthy behaviors such as physical exercise, good sleep habits, proper nutrition and decreased use of alcohol, tobacco and other potentially harmful substances (American Psychological Association, 2019; Gartlehner et al., 2017).

2.2.1 Perinatal depression

The onset of depressive episodes is affected by life stage and significant events, such as pregnancy and childbirth (Brummelte & Galea, 2010). According to a report by the WHO, 10% of pregnant women and 13% of women in the postpartum period suffer from depression (World Health Organization, 2020). Perinatal depression (PND) (or postpartum depression with peripartum onset) is defined as a major depressive episode with onset during pregnancy or in the four weeks following delivery (American Psychiatric Association, 2013). In addition to the effects for the mother, PND also negatively affects the health and well-being of the child (Glover, 2008; Stewart & Vigod, 2016). Even though the risks of PND for both mother and child are well-known, the condition often remains undetected and untreated due to various barriers to help-seeking, such as lack of knowledge, stigma and women being reluctant to take medication during pregnancy and breastfeeding (Bellantuono, Martellini, & Orsolini, 2019; Dennis & Chung-Lee, 2006).

2.3 BIOLOGICAL MEASURES IN RELATION TO STRESS, EXHAUSTION SYNDROME AND DEPRESSION

2.3.1 HPA axis

The hypothalamic–pituitary–adrenal (HPA) axis is one of the biological systems that play an important role in the relationship between stress and ill-health (Iob, Kirschbaum, & Steptoe, 2020; Malhi & Mann, 2018). The HPA axis is activated in response to stress, and the activation leads to an increase in plasma cortisol levels due to a combination of excessive release of cortisol and an impaired glucocorticoid feedback mechanism (Jacobson & Sapolsky, 1991; Menke, 2019). Hence, cortisol has been used as a common biomarker in stress research for many years (Bates, Salsberry, & Ford, 2017; Hellhammer, Wüst, & Kudielka, 2008; Kirschbaum & Hellhammer, 1989) and the association between excessive cortisol levels and mental ill-health on group level has been confirmed in meta-analyses and systematic reviews (Knorr, Vinberg, Kessing, & Wetterslev, 2010; Stetler & Miller, 2011). Despite the evidence of an altered HPA axis activation in stress and depression, no specific lab test of cortisol has been identified for use in clinical diagnosis, nor has any drug yet been approved that targets the HPA axis specifically. Also, there is still a lack of knowledge regarding the association between degree and type of altered HPA axis activation and specific clinical conditions (Menke, 2019; Stetler & Miller, 2011).

2.3.2 Inflammatory biomarkers

Inflammation is an important component of the stress response and is crucial for resolving acute infectious episodes or physical injuries (Furman et al., 2019; Irwin & Cole, 2011). However, prolonged stress seems to cause a chronic low-grade inflammation that in turn could trigger changes of importance in the pathophysiology of stress-related disorders such as depression (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Leonard, 2018; Miller & Raison, 2015). Some inflammatory biomarkers that have been identified as important in the pathophysiology of depression include, for example, interleukin-1β (IL-1β), interleukin-6

(IL-6), interleukin-10 (IL-10), tumor necrosis factor (TNF) and C-reactive protein (CRP) (Köhler et al., 2018; Valkanova, Ebmeier, & Allan, 2013). An increase of inflammatory biomarkers may cause changes in cortical microglia and astrocytes either directly or via afferent nerves, such as the vagal nerves (Dantzer et al., 2008; Malhi & Mann, 2018). This, in turn, may be associated with structural and functional changes in the brain that are related to mental ill-health (Réus et al., 2015).

2.3.3 Heart rate variability (HRV)

During chronic stress, the sympathetic nervous system is often hyperactivated, which is reflected in decreased heart rate variability (HRV) (H.-G. Kim, Cheon, Bai, Lee, & Koo, 2018). HRV refers to the fluctuations of the length of the heart beat intervals (Billman, 2011; Shaffer & Ginsberg, 2017), and is analyzed by using e.g. time-domain and frequency-domain measurements (Shaffer & Ginsberg, 2017). Time-domain indices of HRV quantify the amount of variability in measurements of the interval between heart beats, the time period between successive heartbeats (e.g. Standard deviation of NN intervals, SDNN). Frequency-domain measurements estimate the distribution of absolute or relative power into four frequency bands: ultra-low-frequency (ULF), very-low-frequency (VLF), low-frequency (LF), and high-frequency (HF) bands (Akselrod et al., 1981; Appel, Berger, Saul, Smith, & Cohen, 1989; Camm et al., 1996). HRV has been shown to be reduced also in patients suffering from mental ill-health such as depression or anxiety (Alvares, Quintana, Hickie, & Guastella, 2016; Gorman & Sloan, 2000). In addition, high HRV and the capacity to self-regulate attention, emotions, and behavior has been shown to be correlated (Burg, Wolf, & Michalak, 2012; Nijjar et al., 2014).

2.4 CURRENT TREATMENT OPTIONS

The rehabilitation of patients suffering from stress-related mental ill-health such as exhaustion syndrome and depression encompass several challenges, for example due to the complex etiology and lack of convincing evidence for any specific treatment strategy (Malhi & Mann, 2018; Perski, Grossi, Perski, & Niemi, 2017; Wallensten, Åsberg, Wiklander, & Nager, 2019). In addition to the different interventions described below, psychological interventions such as CBT is recommended for both depression and exhaustion syndrome/burnout (American Psychological Association, 2019; National Institute for Clinical Excellence, 2009; Richardson & Rothstein, 2008; van der Klink, Blonk, Schene, & van Dijk, 2001). Further, workplace-oriented interventions are often a part of exhaustion syndrome rehabilitation (Perski et al., 2017). Also, health care providers are encouraged to promote healthy behaviors such as physical exercise, good sleep habits, proper nutrition and decreased use of alcohol, tobacco and other potentially harmful substances (American Psychological Association, 2019; Gartlehner et al., 2017).

Since the four studies included in this thesis focus mainly on pharmacological treatment and/or MBE and, to some extent, physical exercise, these interventions will be outlined more in detail.

2.4.1 Pharmacological treatment

2.4.1.1 Stress and Exhaustion Syndrome

Currently no evidence-based treatments for stress-related problems such as exhaustion syndrome have emerged, and no psychotropics have been approved as stress-reducing agents (National Board of Health and Welfare, 2003; SBU, 2014a; Willner, Scheel-KrÜGer, & Belzung, 2013). However, many patients receive pharmacological treatment such as antidepressants, anxiolytics, hypnotics and analgesics for symptoms that are more or less associated with stress (Asberg, Nygren, & Nager, 2013; Mojtabai & Olfson, 2011) and the clinical impression is that many patients with exhaustion syndrome obtain antidepressant prescriptions (Osika, 2021).

2.4.1.2 Depression

Pharmacotherapy for depression is mainly based on the monoamine hypothesis, i.e. that depression is associated with a decrease in the levels of the neurotransmitters serotonin, norepinephrine and/or dopamine in the central nervous system (Delgado, 2000; Hirschfeld, 2000; Schildkraut, 1965) even if novel approaches to understand antidepressant drug action are emerging, that include studies on early changes in emotional and social processing and on neural plasticity (Harmer, Duman, & Cowen, 2017). Tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs) are three major groups of antidepressants that all act upon monoaminergic neurotransmission (Willner et al., 2013).

Antidepressants are recommended as part of the standard treatment for moderate and severe depression in adults and are often also included in the treatment of mild depression (National Board of Health and Welfare, 2020; National Institute for Clinical Excellence, 2009). Even though antidepressant drugs in some studies show to be effective in depression treatment (Bollini, Pampallona, Tibaldi, Kupelnick, & Munizza, 1999; Cleare et al., 2015), there is some conflicting evidence regarding their effectiveness in e.g. suicide prevention (Isacsson, 2000; Jorm, Patten, Brugha, & Mojtabai, 2017; Stone et al., 2009).

Further, patients vary considerably in their response to antidepressants, and treatment resistance is often a problem, related to both low or no effect, non-adherence, and under prescription (Crown et al., 2002; Fava, 2003). For example, it has been shown that only one-third of individuals respond fully to antidepressant medication, despite seemingly adequate treatment, including the use of various combinations of drugs (Berlim & Turecki, 2007).

Due to the paucity of reports on strictly defined treatments for refractory depression, a recent review summarized a small number of significant risk factors for treatment resistance, including psychiatric comorbidities, clinical characteristics of the depressive episode, psychosocial factors, biological markers, and the complex nature of the disorder (El-Hage, Leman, Camus, & Belzung, 2013).

Regarding perinatal depression and pharmacotherapy, the main concern is whether the drug increases the risks of teratogenicity or pregnancy complications (Howard et al., 2014; Lusskin et al., 2018). Even though double-blind placebo-controlled studies are lacking, SSRIs, SNRIs and TCAs seem to be acceptably safe, if used correctly during pregnancy and lactation (Howard et al., 2014; Lusskin et al., 2018). Nevertheless, clinicians tend to be more or less reluctant to prescribe antidepressants during pregnancy or lactation (Bellantuono et al., 2019). Also, the women themselves are often reluctant to use antidepressant medication during pregnancy and breastfeeding, due to fear of potential side effects, including addiction both in themselves and their off-springs (Dennis & Chung-Lee, 2006).

2.4.2 Physical activity

The (positive) effects of physical exercise on mental ill-health have been studied during decades and both cross-sectional and longitudinal associations between physical activity and lower risk for depression have been show in several reviews (Chekroud et al., 2018; Currier et al., 2020; Josefsson, Lindwall, & Archer, 2014; Schuch et al., 2018). In line with this research, the UK National Institute for Health and Care Excellence (NICE) guidelines, the European Psychiatric Association and the Swedish National Board of Health and Welfare recommend implementing physical activity as a component in the standard treatment of depression (National Board of Health and Welfare, 2020; National Institute for Clinical Excellence, 2009; Stubbs et al., 2018). Ongoing research is revealing increasing knowledge about beneficial effects of exercise, and about neural mechanisms underpinning these effects (Cervenka, Agudelo, & Ruas, 2017; Ellingsgaard, Hojman, & Pedersen, 2019; S. Kim et al., 2019). However, regarding the efficacy of exercise-related interventions in patients with exhaustion syndrome/burnout there is still no clear evidence. A recent meta-analysis highlights the lack of a stringent intervention concept (Ochentel, Humphrey, & Pfeifer, 2018), and the authors conclude that ‘future studies should deal with the specific efficacy of different exercise modalities and their combination with further cognitive behavioral or mindfulness based interventions’ (Elamin et al., 2020).

2.4.3 Mind and body exercises (MBE)

Mind and body exercises (MBE) are by some researchers defined as interventions combining mental focus, controlled breathing and body movements that are practiced in order to help relax the body and mind (National Center for Complementary and Integrative Health, 2021; Wolsko, Eisenberg, Davis, & Phillips, 2004). MBE are used to improve emotional regulation, body awareness and relaxation (Mehling et al., 2011) and show potential beneficial effects on e.g. stress related symptoms, improved well-being, and reduced emotional reactivity (Lutz, Brefczynski-Lewis, Johnstone, & Davidson, 2008; Sze, Gyurak, Yuan, & Levenson, 2010).

Yoga, tai chi, qi gong and mindfulness, are examples of MBE commonly used to cope with stress-related mental ill-health and with a wide range of depression severity (Barnes, Bloom, & Nahin, 2008; Bertisch, Wee, Phillips, & McCarthy, 2009; D'Silva, Poscablo, Habousha,

Kogan, & Kligler, 2012), these are also included in the questionnaires used in study 1 and 2 in this thesis.

2.4.3.1 Yoga

Yoga is one of the most commonly practiced MBE and its therapeutic potential has been extensively researched during the last 20 years (Bertisch et al., 2009; Cramer, Lauche, & Dobos, 2014; Field, 2016). Yoga has its roots in Indian philosophy and has been a part of traditional Indian spiritual practice for thousands of years (Feuerstein, 2012). Traditionally, it is described as a complex phenomenon including eight 'limbs' (i.e. component, or branches), which are all practiced in order to achieve union of mind, body and spirit. The use of yoga is increasingly popular globally, and mainly physical postures, breathing exercises and meditation are the components of yoga being practiced in Western societies. Even though there are many different forms of yoga (e.g. Hatha yoga, Kundalini yoga and Ashtanga yoga) – which has been highlighted as a problem for research in this field (Field, 2016) – all forms of yoga share common elements.

Several systematic reviews have examined the possible effect of yoga on depression (Cramer, Lauche, Langhorst, & Dobos, 2013; Meyer et al., 2012; Pascoe & Bauer, 2015; Pilkington, Kirkwood, Rampes, & Richardson, 2005; Uebelacker et al., 2010). They all concluded that yoga might be effective for individuals who report elevated levels of symptoms of depression, or who suffer from major depression, but pointed out that is difficulted to suggest yoga based on the current study, as it entails low methodological quality. Inadequate sample size and allocation concealment as well as heterogeneity of yoga interventions are examples of common flaws of the included studies. Cramer et al (2013) emphasize thus the need for more rigorous randomized controlled trials that compare yoga to standard intervention for depression, including psychotherapy or pharmacotherapy (Cramer et al., 2013).

Indeed, for adults with depression for whom psychotherapy or pharmacotherapy is either ineffective or unacceptable, the American Psychological Association (APA) guidelines suggest yoga as an option (American Psychological Association, 2019).

2.4.3.2 Tai chi

Tai chi is closely associated with and considered to be originated from Qi gong, an ancient Chinese holistic practice. Tai chi combines Chinese martial arts and meditative movements, involving a series of dance-like postures that flow into one another in a slow pattern. The movements are combined with a deep diaphragmatic breathing and relaxation and Tai chi practitioners are instructed to focus on their center of gravity and thus maintain their stability. Tai chi has been practiced for centuries in the East, for both fitness and health, and is gaining popularity in the West for the same purposes (F. Wang et al., 2013; Yin & Dishman, 2014).

Even though the research on Tai chi is less extensive compared to research on yoga, the technique has been shown to improve psychological well-being in some studies. Several reviews have been conducted in order to evaluate the effect of Tai chi on

depression/depressive symptoms, mental health and/or stress. The results are not conclusive; one recent review found no significant effect of Tai chi on depressive symptoms (X. Liu et al., 2015) while others found statistically significant improvements in stress, anxiety and depression (C. Wang et al., 2010), anxiety and depression (Yin & Dishman, 2014) and anxiety, depression and stress management (F. Wang et al., 2013). However, regardless of the results, all reviews stated the need for more RCTs with rigorous research designs.

2.4.3.3 Qi gong

Qi gong has its roots in ancient Chinese culture and has been a part of Traditional Chinese Medicine and philosophy for thousands of years. It has been described as a medical exercise, a system of coordinated body postures, breathing and meditation used for health, spirituality and martial arts training. As with yoga, there are different types of Qi gong (e.g. Daoyin Qigong, WuQinXi and BaDuanJin), but even though there are differences among the various forms of Qi gong, they share common elements and all aim to balance 'qi' – often translated as 'life energy' (Cheng, 2015; X. Liu et al., 2015; C.-W. Wang et al., 2014). Compared to Tai chi, Qi gong is considered to focus more on health and medical issues while Tai chi is rather described as a type of Chinese martial art. There are however overlaps between the two systems in regard to body movements as well as purpose (X. Liu et al., 2015).

Several systematic reviews have examined the possible effects of Qi gong on depressive symptoms and other mental health problems and the overall result indicates a significant, favorable effect on depression/depressive symptoms, stress and anxiety (Cheng, 2015; X. Liu et al., 2015; C.-W. Wang et al., 2014; Yin & Dishman, 2014). As for Tai chi, the need for more randomized controlled studies of high methodological rigor in order to evaluate the effect of Qi gong on mental health is highlighted.

2.4.3.4 Mindfulness

Mindfulness has its origin in Buddhist traditions and can be described as a meditation practice that cultivates present moment, non-judgmental awareness, with the aim to disengage from the attachment to beliefs, thoughts and emotions and thereby develop emotional balance and well-being. Mindfulness has been practiced and developed in the East for thousands of years and in the recent 40 years it has become increasingly popular in Western society (Kabat-Zinn, 2006). During this time, certain clinically oriented meditation programs, such as Mindfulness Based Stress Reduction (MBSR) and Mindfulness Based Cognitive Therapy (MBCT), have been developed (Kabat-Zinn, 2006; Segal, Williams, & Teasdale, 2018) and the therapeutic potential of these programs has been extensively researched.

A meta-analysis of mindfulness meditation programs shows significant improvement in anxiety, depression and pain (Goyal et al., 2014). This is consistent with findings from previous meta-analyses and review articles, that indicate a small to medium effect of meditation and mindfulness on the reduction of, for example, stress, anxiety and depression (Chen et al., 2012; Chiesa & Serretti, 2011; Hofmann, Sawyer, Witt, & Oh, 2010; Piet &

Hougaard, 2011). In line with earlier research, a recent meta-analysis shows that MBCT is associated with a significant reduction in the risk of depressive relapse over 60 weeks, when compared with usual care and is equally effective as the current mainstay approach, maintenance antidepressants (Kuyken et al., 2016). The need for trials with active control groups, comparable primary and secondary outcomes, longer follow-ups as well as for cost-effectiveness analyses is however highlighted.

Due to its strong scientific platform, MBCT is recommended for treating Major Depressive Disorder in the NICE guidelines (National Institute for Clinical Excellence, 2009). In the guidelines from the Swedish National Board of Health and Welfare, MBCT is suggested as an approach to prevent depressive relapse in adults and MBSR as an add-on treatment for children and adolescents with moderate to severe depression (National Board of Health and Welfare, 2020).

3 AIMS OF THE THESIS

The overall aim of this thesis was: To map the use of MBE and its associations with health and markers of disease, i.e. prescriptions of psychotropics, and to study if there are any robust effects of MBI on biomarkers of stress, in order to enable evidence-based recommendations and personalized treatment strategies.

As mentioned above, research indicates that MBE may alleviate stress and stress-related symptoms and increase well-being. However, the long-term effects of MBE as well as the association with other treatment strategies, such as pharmacological treatments, are rather understudied. By analyzing data from an established epidemiological cohort including over 18000 participants, combined with prescription data from the Swedish Prescribed Drug Register, this thesis tested the following two hypotheses: 1) Participation in and intensity of MBE practice correlates with improved well-being and alleviated levels of stress; 2) participation in and intensity of MBE practice correlates with decreased levels of medication prescription.

By conducting 1) a meta-analysis on studies of biomarkers (i.e. markers of inflammation and HRV) as outcome measures in mindfulness intervention studies, and 2) a randomized controlled study of the effect of a Mindfulness Based Childbirth and Parenting intervention on similar biomarkers, we aimed to advance and deepen our knowledge about the physiological effects of mindfulness.

The overarching aim was to find out if MBE may be one way to improve health, decrease stress levels and potentially optimize their use with/without simultaneous pharmacological treatment.

3.1 STUDY I

The first study aimed to identify differential associations regarding gender, age, socioeconomic status, health behaviors, perceived stress, self-rated health, and the purchase of prescribed drugs among people who practice MBE extensively compared to people who do not practice MBE.

3.2 STUDY II

The second study aimed to further investigate the *temporal* relationship between MBE, depressive symptoms, purchase of antidepressant drugs and physical exercise, based on the cross-sectional findings in study 1.

3.3 STUDY III

The aim of the third study was to evaluate existing data on the effect of standardized mindfulness based interventions on inflammatory biomarkers and heart rate variability, through a systematic review and meta-analysis.

3.4 STUDY IV

The aim of the fourth study was to investigate the effects of a Mindfulness Based Childbirth and Parenting intervention on HRV and serum inflammatory marker levels in pregnant women, through an RCT study, compared with an active control group.

4 SUMMARY OF THE STUDIES INCLUDED IN THE THESIS

4.1 STUDY I: PREVALENCE OF MIND AND BODY EXERCISES (MBE) IN RELATION TO DEMOGRAPHICS, SELF-RATED HEALTH, AND PURCHASES OF PRESCRIBED PSYCHOTROPIC DRUGS AND ANALGESICS

4.1.1 Methods

The study includes 3,913 men and 4,803 women aged 20-72 years who participated in the Swedish Longitudinal Occupational Survey of Health (SLOSH) in 2012. Measures regarding MBE practice, health behaviors, perceived stress, self-rated health and illnesses were drawn from the SLOSH questionnaire, while more objective measures of socioeconomic status and education were derived from registry data. In addition, data on purchases of prescription drugs for all respondents were included in the study. These data were obtained from the Swedish Prescribed Drug Register, which contains information about prescription drugs dispensed at Swedish pharmacies.

4.1.1.1 Measures

4.1.1.1.1 Questionnaire measures

Mind and body exercises. The use of MBE was measured by asking the participants one single question, 'Do you practice any of the following techniques?'. The question consists of two parts, one regarding physically directed MBE practice (yoga, Tai Chi, Qi gong) and one regarding those with a mental focus (meditation, mindfulness, relaxation techniques). The five response options ranged from 'no' to 'daily'. For the analyses, the respondents were divided into three groups: those who practiced MBE 'never', 'seldom' ('a few times a year' + 'a few times a month'), or 'often' ('a few times a week' + 'daily').

Demographics. Demographic factors such as sex, age, education and socioeconomic status were included in order to investigate possible associations with MBE practice.

Physical activity was assessed with one single question, 'How much exercise do you get? Include any walking or cycling you do to or from work', with four possible response alternatives ranging from 'never' to 'regularly'.

Alcohol consumption/problem drinking was assessed with the CAGE (Cut, Annoyed, Guilty, Eye-opener) questionnaire, which is considered a validated screening technique for identifying alcohol abuse.

Self-rated health was assessed with a single question that has been widely used for research, 'How would you rate your general state of health?'. The respondents answered on a Likert scale, ranging from 1 ('very poor') to 5 ('very good').

Sleeping problems were assessed with the established measures of sleep disturbances (reflecting lack of sleep continuity) and awakening problems (reflecting feelings of being insufficiently restored) by asking six questions about the respondents' sleep habits during the last 3 months, using the Karolinska Sleep Questionnaire.

Pain. The respondents were asked a single question, 'To what extent is pain a health concern for you?'. The extent of pain was scored on a scale from 1 ('minor problem') to 5 ('major problem').

Depressive symptoms were assessed with the Symptom Checklist-core depression scale (SCL-CD6), a six-item scale selected from the Hopkins Symptom Checklist depression subscale. The SCL-CD6 has been found to be a psychometrically valid depression scale which covers six core symptoms of depression (feeling low in spirit, feeling no interest in things, feeling lethargy or low in energy, worrying too much about things, blaming yourself for things, feeling everything is an effort).

Stress was assessed with three items from the Long Lasting Stress scale. The participants were asked how they felt during the past three months with regard to certain symptoms related to stress ('I have days when I feel wound up all the time', 'I have days when I feel very pressured all the time', 'I have days when I feel stressed all the time').

Life satisfaction was assessed by a single item, asking the respondents to specify how satisfied or dissatisfied they were with life in general on a scale from 1 ('very dissatisfied') to 7 ('very satisfied').

Cognitive complaints. The participants were asked about difficulties during the past three months with four symptoms regarding cognitive abilities (concentration, decision making, memory and the ability to think clearly). The scale, ranging from 1 ('never') to 5 ('always'), is originally from The Stress Profile Questionnaire.

Emotional exhaustion symptoms were assessed using the emotional exhaustion subscale of the Maslach Burnout Inventory General Survey, which consists of 5 questions regarding the frequency of the participants' symptoms of burnout. The response alternatives ranged from 1 ('a few times a year or less') to 6 ('every day').

Mental disorders and disease in back, joints, or muscle were assessed by the single question, 'Do you have, or have you had any of the following prolonged and/or severe diseases or complaints/illnesses during the last 2 years, and in that case, how did it affect your life?'. The participants were given four response options: 1 = 'no', 2 = 'yes, but it doesn't affect my life', 3 = 'yes, it affects my life to some extent', and 4 = 'yes, it affects my life a lot'.

4.1.1.1.2 Prescription data

Data from SLOSH questionnaires was supplemented with data on purchases of prescription drugs for all respondents included in the study. This data was obtained from the Swedish

Prescribed Drug Register, which contains information about prescription drugs dispensed at Swedish pharmacies; the drugs are classified according to the Anatomical Therapeutical Classification (ATC) system. The ATC groups included in this study were: N06A (antidepressants), N05B (anxiolytics), N05C (hypnotics), M01A (non-steroidal anti-inflammatory drugs), M02A (topical products for joint and muscular pain), N02B (paracetamol, acetylsalicylic acid), and N02C (antimigraine preparations). ATC groups M01A, M02A, N02B and N02C were included in the same group, referred to as analgesics. In accordance with the Swedish Pharmaceutical Benefits Scheme, patients can purchase a maximum of 90-day supply of prescription drugs intended for continuous use at a time. Thus, all drug purchases within the selected ATC groups ranging from the period of 90 days prior, to 90 days after completing the SLOSH questionnaire were included in the analyses. Based on this information, the participants were classified into two groups depending on whether they had made any purchases of any such drug (regardless of the amount of drug) or not, during the period of interest.

4.1.1.2 Statistical analyses

To test if there were differences between groups with high, medium and low intensity MBE practice in regard to sex, education, having children at home, socioeconomic classification, physical activity, alcohol abuse, smoking, self-rated health, sleep disturbances, awakening problems, diseases, and prescription drugs purchases, Pearson's $\chi 2$ test was used. For age, pain, depressive symptoms, long-lasting stress, life satisfaction, cognitive complaints and emotional exhaustion symptoms, we chose the Kruskal-Wallis test over the one-way ANOVA, since the Bartlett's test showed unequal variances. Separate analyses were performed for mental MBE (mindfulness, meditation, relaxation techniques) and physical MBE (yoga, Tai Chi, Qi gong).

All statistical analyses were performed using STATA software (version 13).

4.1.2 Results

The overall participation rate among the 8,716 respondents in the study population for mental MBE techniques was 15% (n = 1,340), and for bodily MBE was 9% (n = 783).

One of the main findings from the study was in regard to the use of antidepressants among study participants within the different groups of mental MBE. Study participants who practice some form of mental MBE extensively (a few times a week or more often), were three times more likely to purchase antidepressants compared to people who do not practice mental MBE (17% vs 5%). The results were similar for anxiolytics, hypnotics and analgesics. A regular practice of mental MBE was also found to be significantly and positively associated with high scores on the measures of depressive symptoms, long lasting stress, cognitive complaints, emotional exhaustion, sleeping problems, mental disorders and pain, and the findings were consistent with the pattern for prescribed drug purchases. However, no significant differences regarding general life satisfaction were found.

A regular practice of mental MBE was more common among women than men (7% vs 2%) and among physically active than physically inactive people (6% vs 3%).

These cross-sectional associations were similar for bodily MBE. However, the associations were generally stronger for participants in the group practicing mental MBE than for respondents who participate in bodily-directed MBE.

4.1.3 Discussion

This study examined differences regarding, for example, demographics, health behaviors, self-rated health, perceived stress and prescription drug purchase among people who practice MBE extensively, compared to people who do not practice MBE, in a large population-based cohort. The results showed a significant and positive relationship between MBE and *poor* self-assessed health, *high* levels of stress, and psychotropic drug and analgesic purchase.

The significant and positive associations between a regular MBE practice and variables indicating ill-health seen in this study might appear surprising at first, given the positive effects of MBE on stress and stress-related ill-health found in previous studies (Grossman, Niemann, Schmidt, & Walach, 2004; Hofmann et al., 2010). However, this is a cross-sectional study and it is therefore not possible to evaluate causality. Furthermore, the findings from this study are in line with results from several other studies among clinical populations as well as in the general population, confirming a cross-sectional association between MBE practice, poor self-assessed health and high rates of depression or anxiety (Bystritsky et al., 2012; de Jonge et al., 2018; Hanssen et al., 2005; Pilkington & Wieland, 2020; Ravindran & da Silva, 2013; Maria Wemrell et al., 2020). Also, the correlation between MBE practice and gender are in line with findings from other studies (Hanssen et al., 2005; KAM-utredningen, 2019).

The results may partly be explained by the fact that patients suffering from stress-related ill-health such as exhaustion syndrome and depression sometimes are recommended activities like mindfulness by their prescribing physician (National Board of Health and Welfare, 2020; SBU, 2014b). Further, our findings might also reflect that patients use MBE as a way to be active in their own health and treatment, and as a complement to conventional treatment rather than an alternative (Thorne, Paterson, Russell, & Schultz, 2002).

4.2 STUDY II: MIND AND BODY EXERCISES (MBE), PRESCRIBED ANTIDEPRESSANT MEDICATION, PHYSICAL EXERCISE AND DEPRESSIVE SYMPTOMS – A LONGITUDINAL STUDY

4.2.1 Methods

This study was based on respondents from the Swedish Longitudinal Occupational Survey of Health (SLOSH), wave 4 (2012) and wave 5 (2014). To be included, participation in both sweeps was required. In total 7587 persons, 4318 women and 3269 men aged 24-74 years, participated in both 2012 and 2014. Measures of MBE practice, physical exercise and depressive symptoms were drawn from the SLOSH questionnaire, while data on prescription

antidepressant drug purchase (ATC group N06A) for all respondents in the study was obtained from the Swedish Prescribed Drug Register.

4.2.1.1 Measures

4.2.1.1.1 Questionnaire measures

Mind and body exercises. See Methods for study I for details. MBE practice was assessed and used as an ordinal variable from both waves (2012 and 2014) in the structural equation modeling SEM analyses. Physical and mental MBE were considered both separately and jointly in the analyses.

Depressive symptoms. See Methods for study I for details. Depressive symptoms were assessed and used as a continuous variable from both waves (2012 and 2014), the sum score of the six items ranged from 0 to 24.

Demographics. The demographic factors sex, age and education from 2012 were included as potential confounders.

Physical exercise. See Methods for study I for details. Physical exercise was assessed and used as an ordinal variable from both waves (2012 and 2014) in the SEM analyses.

4.2.1.1.2 Prescription data

Data from SLOSH questionnaires was supplemented with data on prescription antidepressant drug purchase for all respondents included in the study. See Methods for study I for details. The ATC group included in this study was N06 A (antidepressants). All antidepressant drug purchases within the selected ATC group during the period ranging from 90 days prior, to 90 days after completing the SLOSH questionnaires (both waves) were included in the analyses.

4.2.1.2 Statistical analyses

Repeated measurements in SLOSH and Swedish Prescribed Drug Register respectively, were used to examine longitudinal relationships between MBE and depressive symptoms/antidepressant purchase by means of structural equation modeling (SEM). Briefly, SEM enables multiple simultaneous regression analyses. In this study, SEM was used to study cross-lagged relationships. Based on earlier research showing that sex, age and education are related to both MBE and depressive symptoms (Clarke, Black, Stussman, Barnes, & Nahin, 2015; Ferrari et al., 2013; Radmark, Hanson, Horwitz, & Osika, 2017), these demographic factors from 2012 were included as potential confounders in the SEM analyses.

In order to further understand the relationship between antidepressants, MBE and depressive symptoms, additional analyses were performed using logistic regression. Antidepressants 2012, MBE practice 2012 and depressive symptoms 2014 were dichotomized and a variable (4 categories) considering MBE and antidepressants separately as well as jointly was created.

These analyses were adjusted for sex, age, depressive symptoms, education and physical exercise from 2012.

All statistical analyses were performed using STATA software (version 13).

4.2.2 Results

Similar to the findings in the cross-sectional study, the practice of MBE was more common among women and among those with higher levels of education.

The main findings from the SEM analysis were:

1) Both MBE practice and antidepressants in 2012 were associated with higher levels of depressive symptoms two years later, with standardized regression coefficients of 0.04 (95% CI0.01, 0.06) and 0.06 (95% CI 0.04, 0.09), respectively.

2) Depressive symptoms in turn, were associated with subsequent higher levels of MBE practice and antidepressants, with standardized regression coefficients of 0.05 for both paths.

However, no statistically significant temporal relationship between MBE and prescription antidepressant purchases was found.

Both depressive symptoms and antidepressants were significantly associated with lower levels of physical exercise two years later, while MBE was significantly associated with subsequent higher levels of physical exercise. Physical exercise in turn, was statistically significantly associated with subsequent lower depressive symptoms and higher levels of MBE, but no statistically significant association with antidepressants was found.

The root mean square error of approximation (RMSEA) and comparative fit index (CFI) both indicated a good model fit and despite the relatively low Tucker-Lewis index (TLI), the model fit was considered acceptable.

The post hoc analysis of depressive symptoms across strata of MBE and antidepressants, showed that only antidepressants were independently associated with depressive symptoms two years later. Antidepressants in combination with MBE was also associated with higher depressive symptoms, but MBE itself was not independently associated with higher depressive symptoms.

4.2.3 Discussion

This study examined the longitudinal relationships between MBE, depressive symptoms, prescription antidepressant purchases and physical exercise and was based on the findings from the first study included in this thesis.

The results from this study clarify, and to some extent replicate, findings from the first study, that showed significant and positive cross-sectional relationships between MBE practice, prescription antidepressant purchases and depressive symptoms (Radmark et al., 2017). In the SEM-analysis, both MBE practice and antidepressants were found to be bidirectionally

associated with depressive symptoms over time, which is consistent with our earlier results as well as with results from several other studies showing an association between MBE practice and high rates of mental ill-health such as depression (de Jonge et al., 2018; Hanssen et al., 2005; Pilkington & Wieland, 2020; Radmark et al., 2017). However, only the association between antidepressants (alone or in combination with MBE) practice and subsequent depressive symptoms was confirmed in post hoc analyses. The temporal association between MBE practice and depressive symptoms could not be confirmed. This and the lack of a statistically significant temporal relationship between MBE practice and antidepressants in the SEM-analysis, might be explained by confounding by indication. Confounding by indication occurs when the clinical indication for selecting a particular treatment (e.g., severity of the illness) is also associated with the outcome (Kyriacou & Lewis, 2016). In this case, it means that those with less severe symptoms of depression may have been more likely treated with MBE only, while those with more severe indications of depression would be treated with antidepressants, sometimes in combination with MBE.

The statistically significant association between physical exercise and subsequent lower depressive symptoms is in line with research indicating positive effects of physical exercise on mental ill-health (Chekroud et al., 2018; Currier et al., 2020; Josefsson et al., 2014; Schuch et al., 2018).

4.3 STUDY III: A SYSTEMATIC REVIEW AND META-ANALYSIS OF THE IMPACT OF MINDFULNESS BASED INTERVENTIONS ON HEART RATE VARIABILITY AND INFLAMMATORY MARKERS

4.3.1 Methods

This study was conducted in accordance with the guidelines suggested by the Cochrane handbook for systematic reviews of interventions (J. P. Higgins et al., 2019), and the findings and procedure were reported in relation to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher, Liberati, Tetzlaff, & Altman, 2010). The protocol was registered in PROSPERO (number 2019 CRD42019136595) and is available online.

The inclusion and exclusion criteria for the original studies included in the systematic review were formulated according to the PICOS components (Population, Intervention, Comparator, Outcome, Study design) and consisted of the following: P – individuals aged 18 years and above regardless of health status (i.e., studies that recruited patients with somatic or psychiatric disorders were considered for inclusion); I – MBI defined as a 6- to 10-week long intervention with weekly meetings of at least 2 h and home practice assignments, and where formal mindfulness practices constituted a central intervention component; C – any type of active comparators (e.g., a control intervention other than MBI) or inactive comparators (e.g., wait-list or treatment as usual); O – inflammatory biomarkers (including pro-inflammatory cytokines and CRP) and HRV frequency domain and time domain parameters; S – randomized controlled trials (RCTs) and non-randomized controlled trials with a matched

control group. Studies were excluded if written in a language other than English, or if no numerical data was available for calculation of the effect size (ES).

A literature search strategy was developed in collaboration with two experienced university librarians. The following electronic databases were searched from inception to November 9th, 2017: MEDLINE (via Ovid), PsychINFO (via Ovid), PubMed, Web of Science, EMBASE, and CINAHL. A grey literature search was conducted in ProQuest (Dissertations and Theses) and ClinicalTrails.gov. Free text or index terms (e.g., Medical Subject Headings) were searched for in titles, abstracts and key words. The use of key words was adapted to each electronic database. In addition, articles were identified through backward and forward hand-search reference chaining.

Literature screening and data extraction were performed independently by two researchers. Any disagreements at the stage of screening or data extraction were resolved through discussion and consulting a third reviewer, if necessary. If multiple outcomes were reported in the same study, quantitative data was extracted separately for each outcome. If data was missing in the original reports, authors were contacted for further clarification.

The methodological quality of included studies was assessed independently by two researchers using the Cochrane Collaboration's tool for assessing risk of bias (J. P. T. Higgins et al., 2011), focusing on the following domains: sequence generation and allocation concealment (selection bias), blinding of participants and providers (performance bias), blinding of outcome assessors (detection bias), incomplete outcome data (attrition bias), and selective outcome reporting (reporting bias).

As there were variations in measurements of outcomes, a standardized mean difference using Hedges' g was chosen as a common effect size (ES). Because the original studies mostly did not report the changes from baseline, we focused on post-intervention measurements for consistency, as suggested by the Cochrane handbook for systematic reviews of interventions (J. P. T. Higgins et al., 2011). Hedges' g were calculated at post-intervention as a difference in means between intervention and control group, divided by the pooled within-group SD and incorporating a correction factor for small sample sizes (Borenstein, Hedges, Higgins, & Rothstein, 2011). Throughout quantitative synthesis, the original direction of scales indicating the improvement of outcomes was kept. Thus, for all inflammatory markers and the HRV measures LF and LF/ HF, ESs below zero pointed to superiority of the intervention group over the controls, while for the other HRV measures such as HF, SDNN, and RMSSD, ESs above zero indicated that the results favored the intervention. For interpretation of Hedges' g , we applied Cohen's convention with the ES defined as small (0.20–0.49), medium (0.50–0.79), and large ($\geq$0.8) (J. Cohen, 1992). We performed meta-analysis separately for each specific originally reported outcome. We used a random-effects model incorporating both within- and between-study variability for quantitative synthesis given the initial assumptions of between-study heterogeneity. Statistical heterogeneity among the studies was evaluated using Q and I2 statistics. For Q statistics, p -value < 0.1 was regarded as representative of statistically significant heterogeneity, and I2 values of 25%, 50%, and 75% indicated low,

moderate, and high heterogeneity, respectively (J. P. T. Higgins, Thompson, Deeks, & Altman, 2003). We conducted leave-one-out influence analysis to assess the potential impact of individual studies on the overall pooled ES by omitting one study at a time (Tobias, 1999). For each outcome with three or more studies included, we assessed the presence of publication bias using funnel plots, Egger's regression asymmetry test (Egger, Smith, Schneider, & Minder, 1997), and the Begg–Mazumdar adjusted rank correlation test (Begg & Mazumdar, 1994).

All statistical analyses were performed using STATA (version 15.1). P -values < 0.05 were considered statistically significant, and all statistical tests were two-sided.

4.3.2 Results

After removing duplicates, 3441 records were available for title and abstract screening. Due to not meeting the PICOS-criteria, 3356 records were excluded and the full-texts of the 85 remaining articles were examined. Out of these, 75 were excluded and a final number of 10 studies were included in the meta-analysis.

The total number of participants was 607 and out of 10 included studies, 9 were RCTs (no randomization was used for allocating patients in one of the studies). Trials were mainly conducted in the USA and Canada, with fewer studies coming from Europe, New Zealand, and South Korea. One study focused on healthy individuals, while the other 9 studies were conducted with persons with some form of ill-health. Regarding comparison group, wait-list control was used in one study, treatment as usual in 6 studies and a CBT group program in 3 studies.

The quality assessment of the included studies is summarized in figure 1:

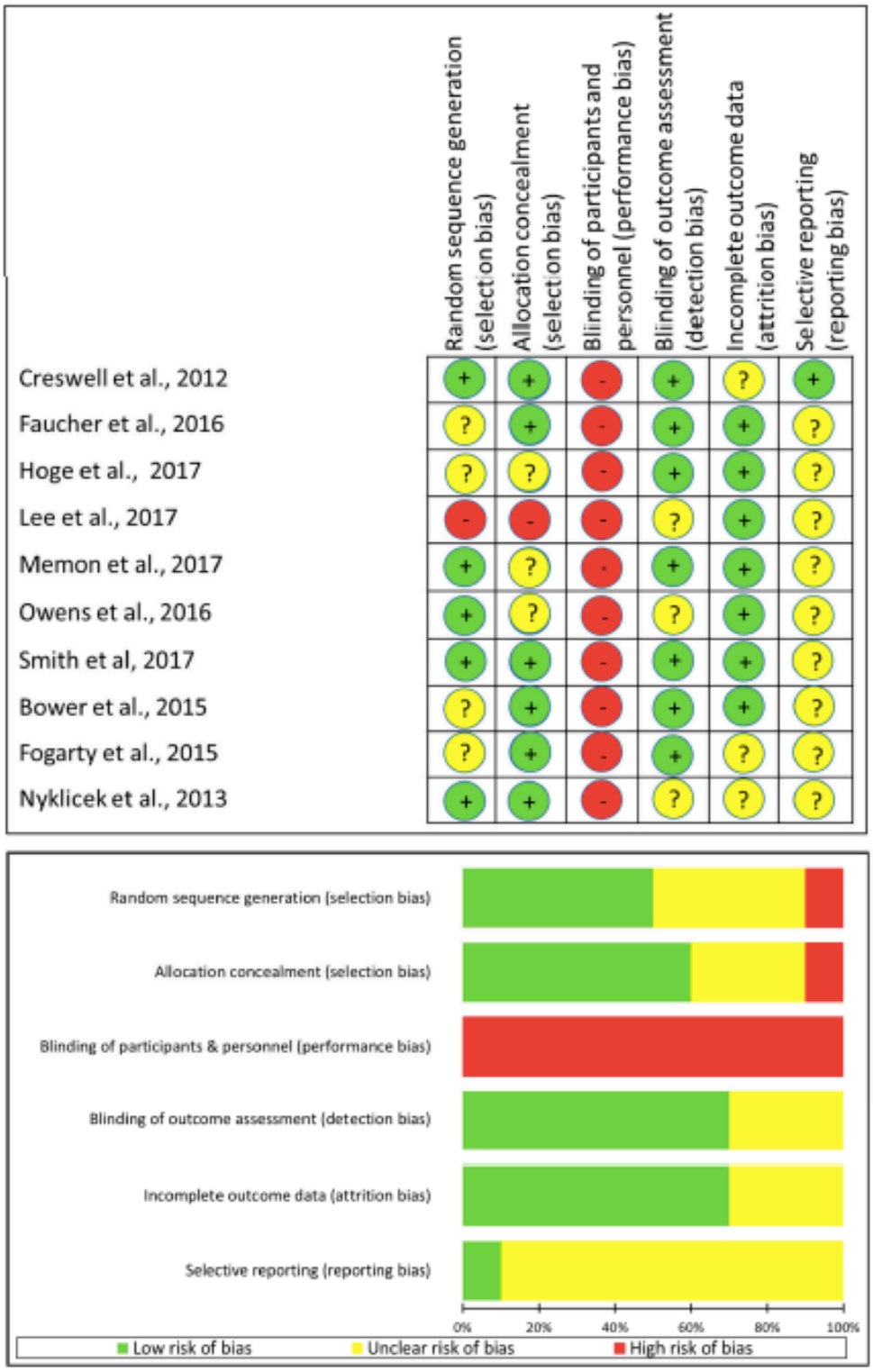

Figure 1. Risk of bias of included studies. From: A Systematic Review and Meta-Analysis of the Impact of Mindfulness Based Interventions on Heart Rate Variability and Inflammatory Markers. Rådmark, L., Sidorchuk, A., Osika, W., & Niemi, M. (2019). Journal of clinical medicine, 8(10), 1638. Open access (Radmark, Sidorchuk, Osika, & Niemi, 2019).

The aggregated results of the included studies on inflammatory markers and HRV measures resulted in very small or small (IL-6, CRP, HF, RMSSD), inconclusive (LF, LF/HF) or medium-sized (SDNN) effects that did not reach statistical significance. No signs of

publication bias were noted for any of the outcomes. No individual studies were seen to influence the pooled results for any of the outcomes, except for the pooled SDNN estimates, for which a study by Nyklicek et al. (Nyklíček, Mommersteeg, Van Beugen, Ramakers, & Van Boxtel, 2013) was found to significantly influence the pooled estimates. Thus, if excluded, the results for SDNN became significant, indicating a favor of control (Hedges' g = -0.99; 95% CI -1.71 to -0.27). Sensitivity analyses revealed no alteration in the main results on IL-6, CRP, LF, HF, LF/HF or RMSSD after exclusion of studies. For SDNN measures, sensitivity analyses revealed a significant reduction if excluding a study on community-dwelling individuals with elevated stress levels (Nyklíček et al., 2013).

4.3.3 Discussion

This systematic review and meta-analysis aimed to evaluate existing data on the effect of standardized mindfulness based interventions on inflammatory biomarkers and heart rate variability.

No significant evidence was found for effects of the standardized MBIs on inflammatory markers or HRV measures, when compared to active controls. The small number of original studies on each specific outcome measure, the small sample sizes of the studies (Flather, Farkouh, Pogue, & Yusuf, 1997), together with the lack of high quality studies (including heterogeneity of mindfulness interventions), probably explain the mixed and inconclusive results.

The results from this study are to some extent contradictory to other existing literature (Black & Slavich, 2016; Morgan, Irwin, Chung, & Wang, 2014; Zou et al., 2018). The differences may be explained by e.g. differences in inclusion criteria, target populations and the content and form (e.g. length) of the MBI programs, between the studies. However, neither one of these other meta-analyses found positive effects of MBIs or mind-body interventions on IL-6, thus paralleling the findings of study III.

4.4 STUDY IV: RANDOMIZED CONTROLLED TRIAL

4.4.1 Methods

This study is a sub-study of a larger RCT, in which first time pregnant women at risk of perinatal depression were randomized to a Mindfulness Based Childbirth and Parenting program (MBCP), or an active control (Lamaze) (Lönnberg et al., 2020). The Stockholm Regional Ethics Committee has approved the study (approval number 2012/400-31/4) and written informed consent has been obtained from all participants. Participants were blinded to the study hypothesis and recruited through eight maternal health clinics in Stockholm County between 2014 and 2015. In total, 86 participants were included in the present study (41 in the intervention and 45 in the control group).

4.4.1.1 Procedure

Eligible participants were informed about the study and scheduled for an appointment at which they gave written informed consent. The baseline questionnaires were filled in on-line and an appointment was made at the maternal health care clinic for HRV-assessment. After completion of the questionnaires, HRV-assessments and having left a blood sample, an administrator, independent of the research team, randomized the participants to either MBCP or Lamaze. The randomization sequence was generated in SPSS in blocks of 10. Participants assigned to the MBCP condition joined the program within two weeks after baseline assessment, and participants who were assigned to Lamaze, joined their program at between three and five weeks after baseline assessment. At ten to twelve weeks after the baseline assessment, both groups completed post-intervention assessments through the same procedure as at baseline.

4.4.1.2 Intervention

The original 9-week MBCP program was developed in the USA and consists of nine 3-hour-long weekly sessions, a full day retreat and a reunion (Bardacke, 2012). In the current trial we adapted the curriculum to the conditions in Sweden, to take account of feasibility, cultural differences and health care settings (see details about these adjustments in Lönnberg et al., 2020).

4.4.1.3 Active control

In order to control for the effects of social support, psycho-education and child-birth preparation, the active control condition consisted of a Lamaze program (AnnasProfylax) that is widely available in Stockholm (for more details see Lönnberg et al., 2020).

4.4.1.4 Outcome Measures

4.4.1.4.1 Questionnaires/psychometric measures

Perceived Stress Scale (PSS). The PSS contains fourteen items that are used to assess perceived stressful experiences in the past month (S. Cohen, Kamarck, & Mermelstein, 1983), and a Swedish version has been translated and validated (Eklund, Bäckström, & Tuvesson, 2014). Participants rate items on a 5-point Likert scale and scores range from 0-56, with higher scores indicating greater perceived stress.

Edinburgh Postnatal Depression Scale (EPDS). The EPDS contains ten items that are used to assess depressive symptoms in the past week. Each item is scored on a four-point scale giving scores between 0 and 30, and with high scores indicating more depressive symptoms (Cox, Holden, & Sagovsky, 1987; Rubertsson, Börjesson, Berglund, Josefsson, & Sydsjö, 2011).

Positive States of Mind (PSOM). The PSOM contains six items that are used to assess positive emotional and cognitive experiences (Adler, Horowitz, Garcia, & Moyer, 1998;

Horowitz, Adler, & Kegeles, 1988). Scores range from 5 to 30, with higher scores indicate a better capacity to experience positive mind states.

Five-facet Mindfulness Questionnaire (FFMQ). The Swedish Version of the FFMQ contains 29 items that are used to assess five facets representing elements of mindfulness (Lilja et al., 2011). Scores range from 29 to 145 and can be divided into sub-scores for each facet (R. A. Baer, Smith, Hopkins, Krietemeyer, & Toney, 2016). High scores indicate a higher capacity for mindfulness. In the larger RCT of which this study is part, we assessed internal consistency for all four scales (Cronbach alpha for PSS = .82, for EPDS = .85, for PSOM = .83, for FFMQ = .85 and FFMQ subscales = .82, .75, .84, .88, .84).

4.4.1.4.2 Serum markers

Prior to randomization, the participants went to a health care clinic laboratory where samples of 5ml blood were collected into serum tubes from each participant. The biological outcomes in this study included serum levels of interleukin-10, osteocalcin and nine acute phase proteins (alpha-2-microglobulin (A2M), C-reactive protein (CRP), haptoglobin, serum amyloid P (SAP), procalcitonin (PCT), ferritin, tissue plasminogen activator (tPA), fibrinogen and serum amyloid A (SAA)). Coefficients of variation were calculated for the manufacturer-provided analytical controls. Samples below the lower level of quantification (LLOQ) were assigned the value of the LLOQ/√2 for the analyses.

4.4.1.4.3 Heart rate variability

ECG registration was carried out in a supine position on a stationary bench. Three ECG electrodes were placed over the left fifth intercostal space, the right fifth intercostal space and over the manubrium, respectively. The ECG signal was inspected for consistency and the level of noise before a minimum 5 minutes of recording was obtained. The ECG-registrations were recorded at a sampling frequency of 1000 Hz and stored on a computer. Each 300 s ECG-recording was inspected by the software for ectopic beats and artifacts, as well as for the correct identification of each R-peak, and non-sinus beats and other artifacts were corrected by interpolation. After preparation of the data, time domain measures of HRV such as SDNN and RMSSD were computed. Also, power spectral analysis was conducted of the frequency domain that partitions the total variance (the 'power') of a continuous series of beats into its frequency components; Low Frequency (LF), 0.04–0.15 Hz, High Frequency (HF) 0.15–0.4 Hz, and the ratio of LF to HF (LF/HF).

4.4.1.5 Statistical Analyses

Independent sample t-tests were used for data that was parametrically distributed on interval scale level. If not, Mann-Whitney U test were used to compare groups. Variables on nominal levels were tested by Fisher´s exact test. Some of the variables were skewed and therefore ln-transformed before analysis with parametric tests could be conducted. Those analytes that had more than 10% of values with LLOQ were transformed into binary variables, where 0 denoted 'under LLOQ' and 1 denoted 'over LLOQ'. Spearman rank correlations (Rs) were

calculated to assess the correlations between the questionnaire target variables and blood sample/HRV target variables at baseline. Within group comparisons from pre- to postintervention were carried out using either paired t-tests for parametric distributions or Wilcoxon signed-rank tests for non-parametric distributions. Linear regression analyses (or multinomial logistic regression analyses for categorical variables) were conducted to assess whether there were any significant differences between the intervention and control group in the change in target variables (post-intervention values minus pre-intervention values). Due to the fact that the participating women entered the study (and hence, the pre-test) at different stages of pregnancy, the regression analyses were adjusted for pregnancy week, since both serum inflammatory markers and HRV are considered to be related to gestation progress. The regression analyses for psychometric measures were not adjusted for pregnancy week, since pregnancy week was found not to be a confounder in the exploratory analyses. Only data from participants who completed the follow-up assessments was analyzed.

All analyses were performed using STATA software (version 14.2).

4.4.2 Results

No significant differences regarding demographic variables or prescribed drug use at baseline were found, and a-2-microglobulin was the only outcome measure significantly differing between groups at baseline, with higher levels in the intervention group.

There was a significant correlation between PSS and osteocalcin at baseline, but no other correlations between the questionnaire target variables and inflammatory biomarkers/HRV measures at baseline were found.

In both groups, the within-group comparisons from baseline to post-intervention showed significant decreases in PSS and EPDS, and significant increases in PSOM and FFMQ. Further, significant increases from baseline to post-intervention serum levels of haptoglobin, serum amyloid P, tissue plasminogen activator and osteocalcin were found in both intervention and control group. A significant increase in serum levels of fibrinogen was found in the control group. No other target variables showed significant changes from baseline to post-intervention in either group.

The intervention group reported a larger reduction in PSS and a larger increase in FFMQ. No other target variables showed significant differences in change from pre- to postintervention between the intervention and control group.

4.4.3 Discussion

This study investigated the effects of a Mindfulness Based Childbirth and Parenting intervention on HRV and serum inflammatory marker levels in pregnant women, through an RTC study, compared with an active control group.

No significant differences were found between the MBCP and Lamaze group, between pre- and postintervention. This could theoretically be due to that both interventions conferred

similar effects on the outcome measures, or that both interventions lacked an impact on the outcome measure. Nevertheless, the results from Study IV are in line with the findings from study III in this thesis, where no uniform evidence on the effect of standardized MBIs on inflammatory markers and HRV parameters could be stated (Radmark et al., 2019).

A normal pregnancy is related to remarkable and complex adaptations in the immune system as well as in the autonomic nervous system, which in turn results in changes in HRV measures (Bränn, Edvinsson, Rostedt Punga, Sundström-Poromaa, & Skalkidou, 2019; La Rocca, Carbone, Longobardi, & Matarese, 2014; Stein et al., 1999). Hence, the results from this study regarding inflammatory markers and HRV respectively, in both groups, might reflect the normal shifts that occurs in pregnancy.

The significantly larger reduction in perceived stress and significantly larger increase in mindfulness in the MBCP group compared to the Lamaze group found in this sub-study, is in line with the findings from the main study (Lönnberg et al., 2020), as well as with previous findings indicating a positive impact of MBI´s on perceived stress and mindfulness in the perinatal period (Badker & Misri, 2017).

5 GENERAL DISCUSSION

This thesis aimed to map the use of MBE and associations with self-assessed health and markers of disease, i.e. prescriptions of psychotropics, and to study if there are any robust effects of MBIs on biomarkers of stress, in order to enable evidence-based recommendations and personalized treatment strategies.

The results from the first two studies included in this thesis showed a significant, cross-sectional association between frequent MBE practice, high levels of depressive symptoms and prescribed antidepressant purchases. When using SEM-analyses followed by post hoc analyses to further understand these relationships over time, the interpretation was not straightforward. Both MBE practice and antidepressants were found to be temporally and bidirectionally associated with depressive symptoms in the SEM-analyses. However, the association between MBE practice and subsequent depressive symptoms could not be confirmed in the post hoc analyses. This, and the lack of a statistically significant relationship between MBE practice and subsequent antidepressant medication found in the SEM-analyses, could be explained by confounding by indication – those with less severe depressive symptoms may be more likely to use MBE as the only treatment, while those with more severe depressive symptoms probably use antidepressants, alone or in combination with MBE.

The cross-sectional findings are in line with several other studies, where associations between poor self-assessed health, high levels of depressive symptoms and MBE practice have been confirmed (de Jonge et al., 2018; Hanssen et al., 2005; Ravindran & da Silva, 2013). These associations might reflect that individuals suffering from ill-health such as mental distress or depression tend to seek more help than others, as described in Andersen´s Behavioral Model of Health Services Use – an established model for conceptualizing professional help-seeking (Ronald M Andersen, 1995; R. M. Andersen, 2008; Graham, Hasking, Brooker, Clarke, & Meadows, 2017). According to Andersen´s model, three predicting factors for help-seeking have been identified; need (perceived as well as evaluated), predisposing factors (personal, social and cultural factors) and enabling factors (organizational factors that affect the availability and affordability of health care). Poor self-assessed health, high levels of depressive symptoms and prescribed psychotropic purchases can be seen as 'need factors' and hence predict help-seeking behavior, such as participating in MBE. The use of MBE as an add-on to pharmacotherapy is also in line with earlier research describing the use of complementary and alternative methods/CAM (such as MBE) as a way for the patient to engage in an take responsibility for their own health and treatment, and as a *complement* rather than an *alternative* to conventional treatment (Thorne et al., 2002; M. Wemrell, Merlo, Mulinari, & Hornborg, 2017). The associations between MBE practice, gender and education are also in line with other studies on CAM-use (Hanssen et al., 2005; KAM-utredningen, 2019) as well as with other studies using Andersen´s model (van Zoonen et al., 2015), showing that women are more likely than men to seek medical help and that education is important in the help-seeking process.

The findings from the longitudinal study clarify the cross-sectional results and add some new information regarding the temporality of the relationships. For example, the results indicate no predictive effect of MBE practice on subsequent antidepressant medication and the temporal associations between MBE practice and depressive symptoms could be explained by confounding by indication. Hence, the results do not imply a negative effect of MBE practice – which was a possible interpretation of the results in study I.

The results from study III and IV in this thesis showed no significant effects of standardized mindfulness based interventions on biological markers of stress and depression (inflammatory biomarkers and HRV) when compared to active controls, treatment as usual or wait-list controls, in a systematic review and meta-analysis and in a randomized controlled study, respectively. Regarding the findings from the meta-analysis, the lack of significant effects might be explained by, for example, the small number of studies for each outcome and a lack of high-quality studies. These are common limitations when conducting a meta-analysis (Lee, 2019; Stevens & Wu, 2007) and the scarcity of evidence regarding physiological measures have been highlighted in similar meta-analyses in the field (Black & Slavich, 2016; Morgan et al., 2014). However, despite these limitations a meta-analysis can contribute with valuable information to the field – like in this case, they may direct and define future research. As for the randomized controlled study, the lack of significant effects of MBCP when compared to the Lamaze program could possibly be due to that both interventions conferred similar effects (or lack of effects) on the biological outcome measures, and that the similar changes in both groups over time hence might reflect the normal shifts that occurs in pregnancy (Bränn et al., 2019; La Rocca et al., 2014; Stein et al., 1999). Additionally, due to the scarcity of other studies in the field, as found in the meta-analysis, it was not possible to conduct a sample size calculation for the present study which in turn could potentially explain the lack of significant results.

This thesis, and the findings from the studies included, can be discussed in terms of patient-centered care (PCC) or shared decision-making between patient and physician – with focus on mental health issues such as exhaustion syndrome or depression. It has been shown that both patient and prescriber influence adherence to, for example, antidepressant medication (van Dijk et al., 2007). This has led to the development of shared decision-making as an important tool in the mental health field, which is thus considered a crucial component of PCC (Grim, Rosenberg, Svedberg, & Schön, 2016; Zaini et al., 2018). In addition to shared decision-making, communication and support for self-management have been described as key elements of PCC (Robinson, Callister, Berry, & Dearing, 2008). The potential benefits of using complementary methods such as MBE, as a part of PCC, have been highlighted (Foley & Steel, 2017), and efforts have been made to integrate e.g. MBE in conventional healthcare institutions in Sweden (KAM-utredningen, 2019; National Board of Health and Welfare, 2020; Maria Wemrell et al., 2020) as well as globally (de Jonge et al., 2018; Horrigan, Lewis, Abrams, & Pechura, 2012; World Health Organization, 2013). This is in line with the current use of MBE as a complement to conventional treatment (de Jonge et al., 2018; Thorne et al., 2002; M. Wemrell et al., 2017) as well as with patients' wish for increased cooperation

between complementary and conventional care and for a possibility to openly discuss their use of complementary care with conventional health care professionals (M. Wemrell et al., 2017; Wode, Henriksson, Sharp, Stoltenberg, & Hök Nordberg, 2019). In order to be able to openly discuss the care that their patients are receiving - whether conventional or not - health care professionals need more knowledge about the most commonly used complementary methods, such as MBE, including the current *scientific evidence* for the different methods, *how* they are used and for *what reasons*. One way of increasing the knowledge about complementary methods among health care professionals is to include this field in the education of health care students, as proposed in e.g. the Swedish governmental investigation (KAM-utredningen, 2019). Moreover, in addition to information targeting ill patients, 'healthy people' also need health-related information to be able to participate in health-related decisions, e.g. to decide whether they should participate in prevention interventions (Pieper et al., 2015).

5.1 STRENGTHS

This thesis has several strengths. The included studies examine MBE, with a focus on mindfulness based practices, in different populations and with a variety of methods. Hence, it gives a broad and nuanced perspective on the topic - an approach that is recommended in recently suggested research agendas (Davidson & Dahl, 2018; Van Dam et al., 2018).

Regarding the strengths of the included studies, study I and II are based on SLOSH – a large and approximately nationally representative sample of the Swedish working population, allowing broad generalizability of the results. In addition to self-reported data, study I and II also include data from the Swedish Prescribed Drug Register, one of the largest population-based pharmacoepidemiological databases in the world. The register covers all prescription drugs and provides thus robust data for descriptive and analytical studies. Study I contributes to increasing knowledge about the use of MBE in the general population and about the cross-sectional association of MBE practice with for example depressive symptoms and antidepressant medication. Study II provides new information about the temporality of those associations.

Study III and IV both give information about the not-so-well-researched field of the effects of standardized MBI´s on inflammatory biomarkers and HRV. A general strength of meta-analyses is that they provide a more precise estimate of the effect size and increase the generalizability of the results of individual studies. A strength of the RCT is the randomization and comparison with an active control group.

5.2 LIMITATIONS

This thesis has also some limitations, related to methodological considerations for each included study.

In study I, the study design is cross-sectional, hence, no conclusions regarding causality can be drawn. Further, study I and II also share some similar limitations. First, the questions

regarding MBE practice are broad and do not give detailed information about *how* the MBE was practiced (on one´s own at home, in a group led by an authorized instructor etc.). Neither do they contribute with information on which form of yoga, Tai chi, mindfulness etc. are being practiced (e.g. standardized MBI or not). It is also possible to regard yoga, tai chi and Qi gong as both MBE and as physical exercise, and it might be problematic to separate these two activities. This, in turn, might affect the results in study II in particular. Furthermore, even though the prescription data is robust, prescription drug purchase is not a direct indication of prescription adherence. In addition, not everyone diagnosed with depression is treated with antidepressants (which can result in an underestimation of the prevalence of depression). Sometimes, antidepressants are used for other indications (such as premenstrual syndrome), while sometimes overtreatement also occurs. Thus, the relationship between diagnosis, prescribed drug purchases and intake of the drugs is not straightforward. A relatively large group declined to respond to the SLOSH survey which is not optimal. If the non-response is selective, it might affect the relationships studied. As people who were originally working are followed up over time, the non-working population is also underrepresented in the SLOSH sample.

The main limitation in study III, the meta-analysis, is the small number of studies evaluating the effects of standardized MBIs on inflammatory biomarkers and HRV measures. This affected the analysis especially of HRV parameters, and it was also not possible to assess the moderating effect of for example gender and age. Furthermore, there was a variation in quality of the original studies – with performance bias being the most common variation.

The scarcity of studies mentioned above, also made us unable to conduct a sample size calculation for study IV, which is an obvious limitation. Due to the large number of statistical analyses conducted in the study, significant changes in certain variables should be interpreted with caution. Indeed, a Bonferroni correction for multiple comparisons would render the correlation that we detected between Osteocalcin and PSS non-significant.

5.3 IMPLICATIONS OF THE FINDINGS

The findings in this thesis demonstrate the quite widespread use of complementary methods, such as MBE, that occurs in parallel with frequent use of psychotropics among a stratified selection of the general working population as well as in clinical populations. This finding emphasizes the need for increased knowledge among medical practitioners about complementary methods and the simultaneous use of e.g. psychotropics, in order to enable a well-informed dialogue/communication with patients. Further, the findings also highlight the inconclusive evidence on the biological/physiological effects of MBIs. While the amount of research on MBIs and other complementary methods has increased, there is still a need for both experimental studies in order to delineate mechanism of (in)action, and robust RCT studies, with active control groups, in order to provide health care professionals with scientifically validated information.

5.4 FUTURE DIRECTIONS

Through this thesis work, different perspectives on the use of MBE practice have been explored, and in the light of the findings some future research questions are suggested.

The findings in study III, and to some extent study IV, highlight the necessity of larger, more rigorously conducted RCTs with standardized MBIs being compared to various forms of active controls, also including more long-term follow-ups. It may also be of interest to conduct future RCTs among pregnant women, where a third arm without any intervention is included in order to take into account the normal shifts in biomarkers that occurs in pregnancy.

The temporal relationships between MBE practice, depressive symptoms and antidepressant medication (and preferably also other treatment methods, e.g. psychotherapy) need to be examined more in detail and over a longer period of time in order to answer questions like: might participation in MBE increase depressive symptoms in some participants? And/or is it that participants undertake MBE because of depressive symptoms, and would be even worse off without MBE practice? Should MBE be avoided or preferred in any sub-groups, or during specific situations? Are there particular combinations of treatments that are favorable, or on the contrary, doubtful? Even though the associations between MBE and depressive symptoms found in study I and II might be explained by confounding by indication, and hence do not necessarily indicate a negative effect of MBE practice, it is highly desirable to explore possible negative experiences of MBE in future research, using e.g. RCTs. The need for systematic screening of side/adverse effects of MBE has been highlighted in several articles during recent years (Davidson & Dahl, 2018; Van Dam et al., 2018). Despite the growing number of studies on the topic (R. Baer, Crane, Miller, & Kuyken, 2019; Cebolla, Demarzo, Martins, Soler, & Garcia-Campayo, 2017; Farias, Maraldi, Wallenkampf, & Lucchetti, 2020; Lindahl, Fisher, Cooper, Rosen, & Britton, 2017), the field is still under-researched.

6 CONCLUSIONS

This thesis explored the use of MBE and its associations with self-assessed health and psychotropic medication and investigated if there are any distinct patterns regarding the effect of MBIs on biomarkers of stress and depression.

MBE practice was found to have significant cross-sectional associations with high levels of depressive symptoms and prescribed antidepressant purchases. The temporal investigations of these relationships revealed a more complex picture, where MBE practice itself was not associated with either subsequent antidepressant medication or with subsequent depressive symptoms. To be able to learn more about these correlations, further research is needed.

No significant effect of standardized MBIs on inflammatory biomarkers and HRV, when compared to active controls, treatment as usual or wait-list controls, was found – neither in the meta-analysis nor in the randomized controlled study. The lack of association might be due to a true weak impact of MBIs on the chosen outcome measures in the studies performed. In order to gain more certainty about the effects of MBI on biomarkers, more rigorously conducted RCTs on the topic including larger sample sizes, would be needed.

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