Dissertation

Sex and Depression: Understanding the Gender Gap in Symptomatology, Course of Disease and Therapeutic Response

submitted by

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Statutory Declaration

I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all of those individuals and organizations that have contributed to the research for this thesis. Due acknowledgement has been made in the text to all other material used. Throughout this thesis and in all related publications I followed the ***Standards of Good Scientific Practice and Ombuds Committee at the Medical University of Graz****.*

Karin Schwalsberger - eh

Disclosures

This thesis was written at the doctoral school “Lifestyle-related diseases”.

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Table of Contents

Abbreviations

BDI-II	Becks Depression Inventory II
BDNF	brain-derived neurotrophic factor
BFI-10	Big Five Inventory
BMI	Body mass index
CRH	Corticotropin-releasing hormone
DD	Depressive Disorders
HAMD	Hamilton Depression Scale
HPA-axis	Hypothalamic pituitary adrenal axis
ICD	International classification of diseases
IDO	indoleamine 2,3-dioxygenase-1
Kyn	Kynurenine
M	Mean
MANOVA	Multivariate analyses of variances
MAO	Monoamine oxidase
N	Number of patients
SD	Standard deviation
SSRI	selective serotonin reuptake inhibitors
SVF-78	Stress Management Questionnaire [Abbreviation of German term]
T1	Time of admission / first measuring point
T2	Time of discharge / second measuring point
TPH	Tryptophan hydroxylase
Trp	Tryptophane

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Abstract

Introduction: Gender and sex-related medicine, as well as personalized care, is of tremendous importance. To ensure personalized treatment in depressive disorders (DD) it is essential to investigate potential differences between women and men with DD. The aim of this study was to investigate sex-related differences in DD regarding classic psychological key variables (Big Five personality traits and coping styles), physiological comorbidities, inflammatory biomarkers, and pharmacological treatment (number and kind of drugs). Furthermore, sex-related differences in treatment response after a six–week rehabilitation program were examined and determinates of the severity of depression were investigated. *Method*: The data of 388 patients (194 females) — matched by age and severity of depression — participating in a psychiatric rehabilitation program were analyzed. Psychological and physiological variables were assessed before and after a six-week rehabilitation program and were compared between women and men. *Results*: Females showed higher scores in the Big Five personality traits, especially Neuroticism, and displayed unhealthy stress coping styles compared to men. Men more often suffered from cardiovascular diseases and women from thyroid dysfunction and food intolerances. Positive changes due to the rehabilitation program were found in women and men; however, the changes where more profound in women. *Discussion/Conclusion:* Differences in the response towards stressful events between women and men might be associated with personality traits and coping strategies according to the results of this study. Different health issues were found to be especially relevant for men (i.e., cardiovascular diseases) and others for women (i.e., thyroid dysfunction or physiological stress response). Women appeared to experience more positive changes during the rehabilitation program. The findings should be taken into account when realizing personalized treatment.

Keywords: major depression, sex-related differences, personalized care, physiological comorbidity, polypharmacy

Abstract – German

Einleitung: Gender- und geschlechtsbezogene Medizin sowie personalisierte Behandlung sind von enormer Relevanz. Um eine personalisierte Therapie bei einem depressiven Störungsbild zu gewährleisten, ist es wichtig, potentielle Unterschiede zwischen Frauen und Männern mit depressiven Symptomen zu untersuchen. Ziel dieser Studie war es, geschlechtsspezifische Unterschiede hinsichtlich psychologischer Schlüsselvariablen (Big Five Persönlichkeitsmerkmale und Coping-Strategien), physiologischer Komorbiditäten, inflammatorischer Biomarker und pharmakologischer Therapie (Anzahl und Art der Medikamente) bei diesen Patient*innengruppen zu untersuchen. Weiters wurden geschlechtsspezifische Unterschiede im Ansprechen auf eine sechswöchige Rehabilitationsbehandlung untersucht und Determinanten der Schwere der Depression eruiert. *Methode:* Die Daten von 388 Patient*innen (194 Frauen) – gematcht nach Alter und Schweregrad der Depression – die an einem psychiatrischen Rehabilitationsprogram teilnahmen, wurden analysiert. Psychologische und physiologische Variablen wurden vor und nach einem sechswöchigen Rehabilitationsaufenthalt bewertet und zwischen Frauen und Männern verglichen. *Ergebnisse:* Frauen zeigten höhere Werte in den Big Five-Persönlichkeitsmerkmalen, insbesondere Neurotizismus, und zeigten im Vergleich zu Männern schädlichere Stressbewältigungsstrategien. Männer litten signifikant häufiger an Herz-Kreislauf-Erkrankungen und Frauen an Schilddrüsenfunktionsstörungen und Nahrungsmittel-unverträglichkeiten. Positive Veränderungen aufgrund des Rehabilitationsprogramms wurden bei Frauen und Männern festgestellt, jedoch waren die Veränderungen bei Frauen tiefgreifender. *Diskussion / Conclusio:* Die Ergebnisse dieser Studie deuten drauf hin, dass aufgrund von Persönlichkeitsmerkmalen und Bewältigungsstrategien Frauen und Männer unterschiedlich auf stressauslösende Ereignisse zu reagieren scheinen. Weiters wiesen Männer (Herz-Kreislauf-Erkrankungen) und Frauen (Schilddrüsenfunktionsstörungen und physiologische Stressreaktion) unterschiedliche gesundheitliche Problemschwerpunkte auf. Frauen erfuhren mehr positive Veränderungen durch das Rehabilitationsprogramm im Vergleich zu Männern. Die Erkenntnisse sollten bei der Realisierung einer personalisierten Therapie berücksichtigt werden.

Schlüsselwörter: Depression, geschlechtsspezifische Unterschiede, personalisierte Versorgung, physiologische Komorbiditäten, Polypharmazie

1 Introduction

1.1 Theoretical background

In the last 20 years, gender or sex-related medicine has become an increasingly important area of research. To some extent, sex-related differences can be found in every field of medicine and every disease or illness. For example, a higher prevalence of asthma, cancer, and chronic obstructive pulmonary disease can be found in men (1). In myocardial ischemia, women present more symptoms beyond chest pain, such as dyspnea, nausea, or fatigue than men (2). Body mass index (BMI) was specifically highlighted as a sex-dependent risk factor for somatic disease (3).

In psychiatry, sex differences in illness presentation have been found as well. For example, in schizophrenia, male patients have an earlier onset, more negative symptoms, and the course of the disease is less favorable with more substance abuse compared to women (4–6). In women schizophrenia presents itself more often with depressive symptoms and hallucinations. Furthermore, estrogen seems to be a psycho-protective factor in women, hence the later onset (6). Another example is bipolar disorder. The prevalence of this mental illness is similar in women and men; however, women have a higher risk for a rapid cycling and might be at a higher risk of antidepressant-induced rapid cycling (7, 8). Furthermore, women are at a higher risk of suffering from a postpartum episode (7, 8) and more often have comorbid thyroid disease and post-traumatic stress disorders (9). Despite plentiful research in the field, the cause and characteristics of sex differences found in mental disorders have not been sufficiently elucidated yet.

Depressive disorders (DD) are among the most common psychiatric disorders (10). This severe psychiatric disease group is accompanied by life-threatening symptoms and individual suffering. It has a tremendous effect on national health care systems and society in general. Among the most severe symptoms of DD are suicidal thoughts and suicide. Globally, about 800,000 people commit suicide every year. In the age group of 15-29, suicide is the second leading cause of death (11, 12). Women are found to have a 1.5 to 2 times higher risk of developing a DD than men. This sex-specific gap in DD is well established but cannot be fully explained yet (13). Beside biological and sociocultural factors, differences in psychological variables such as personality traits and coping strategies between women and men could be factors influencing this gap. Additionally, DDs are often accompanied by different somatic and

psychiatric comorbidities which often lead to depraved health conditions (14–16). These comorbidities are associated with severe course and symptoms (14) and seem to vary depending on the sex of the individual (15). Little research has been done in the field of sex-related differences in somatic comorbidities in patients with a DD. Due to the plentiful comorbidities, patients with DD often hold a high number of different medications. Little research has been completed on sex-related differences concerning polypharmacy in patients with DD. Gaining information about sex-related differences in these areas can help to achieve an optimized personalized treatment. In that sense, it is also of relevance to investigate whether existing psychiatric treatment programs have different effects on a patient depending on their sex.

The study described in this dissertation aims to investigate the above-mentioned sex differences of patients with depressive symptoms. The study is part of a larger study project called "The Neurobiological Foundation of Burnout Syndrome" with its main goal of investigating the psychological and neurobiological foundation of affective disorders, with a special focal point on burnout syndrome and its discrimination from affective disorders. This main study project (EK number, E-24-14) was conducted in a psychiatric rehabilitation clinic in upper Austria where the author of this dissertation was the study coordinator. For more information about the main study see the paper of Reininghaus et al. (16).

1.2 Depressive disorders – etiology, prevalence, sex differences

As one of the most common groups of diseases in the Western hemisphere, DD are a significant health-threatening factor (17). In Austria the prevalence of DD in the adult population is estimated to be between 9.9% to 15.6% (18). According to the World Health Organization it is estimated that more than 264 million people suffer from DD worldwide (11).

The International Classification of Diseases - 10th Revision (ICD-10 (19) characterizes unipolar affective disorders as follows:

In typical mild, moderate, or severe depressive episodes, the patient suffers from lowering of mood, reduction of energy, and decrease in activity. Capacity for enjoyment, interest, and concentration is reduced, and marked tiredness after even minimum effort is common. Sleep is usually disturbed and appetite diminished. Self-esteem and self-confidence are almost always reduced and, even in the mild form, some ideas of guilt or worthlessness are often

present. The lowered mood varies little from day to day, is unresponsive to circumstances and may be accompanied by so-called "somatic" symptoms, such as loss of interest and pleasurable feelings, waking in the morning several hours before the usual time, depression worst in the morning, marked psychomotor retardation, agitation, loss of appetite, weight loss, and loss of libido. Depending upon the number and severity of the symptoms, a depressive episode may be specified as mild, moderate or severe.
This includes single episodes of depressive reaction, psychogenic depression, or reactive depression and excludes adjustment disorder (recurrent depressive disorder (F33.-), and when associated with conduct disorders in F91.- (F92.0) (19).

In order to be diagnosed with a depressive episode an individual must show at least four of the listed symptoms, and these must include at least two of the key symptoms labelled with *. The symptoms for a depressive episode include:

- *Depressed mood
- *Anhedonia / loss of interest and enjoyment
- *Energy loss / Reduced energy leading to: increased fatigability and / or diminished activity
- Reduced concentration and attention
- Reduced self-esteem and self-confidence
- Ideas of guilt and unworthiness
- Bleak and pessimistic views of the future
- Ideas of acts of self-harm and / or suicide
- Disturbed sleep
- Diminished appetite

Depressive episodes can be a one-time only event or reoccurring, and may occur with or without psychotic symptoms (19).

1.2.1 Lifetime prevalence

Weismann and colleagues were among the first to find scientific evidence for sex differences in DD (20). They ascertained, that women suffer from a DD about twice as often as men do. Many other scientists have followed this research path and found equivalent results (21–26). For an overview, see the meta-analysis by Salk and colleagues (27). Kessler at al. found in 1993

that women have an approximately 1.7 times higher risk of suffering from a DD, replicating their own findings in 2005 by surveying over 9000 English-speaking individuals and finding that women have a 1.5 times higher chance of having an mood disorder (22, 23). This 1.5 to 2 times higher rate of depression in women is widely recognized (13). This difference is found in all cohorts from early adolescence to late fifties. It is especially dominant in the younger cohorts (28, 22). Interestingly, this difference cannot be found in childhood, where research results show either no difference or a slight preponderance to depressive symptoms among boys (29–31). The sex difference seems to appear with puberty and rise substantially until the age of 18 (32–34). Some studies found that the difference diminishes after menopause. There is some evidence that the DD rate among men rises above the rate among women after that age (21, 35, 28, 36), but most studies found the gender gap in DD to persist into late life (37, 38).

In regard to the chronicity, remission, and acute recurrence rate of patients suffering from a DD, there is no evidence of sex-related differences. The main difference in the presentation of DD in males and females appears to be that women have an earlier first onset compared to men. Women are about 1.5 times more likely to develop depression once in their life compared to men. The probability of a recurrence of a depressive episode is similar in women and men (22, 24, 39–41).

1.2.2 Etiology of DD

It is well established that the development of a DD is the result of the interaction of biological, psychological, and sociological factors. Comparable to most psychiatric disorders, the Diathesis Stress Model (see Figure 1 and Figure 2) explains the etiology of depressive symptoms. Genetic factors, as well as physical conditions (inflammation, cardiovascular diseases, endocrine processes, etc.) play a crucial role in developing depression, along with psychological determinants (early childhood trauma, cognitive attribution styles, parental upbringing, etc.) and social factors (life events, stress, work load, etc.) (42, 43). These three factors influence each other and can either facilitate or help to prevent the development of depressive symptoms. In addition, these factors cannot be separated from each other.

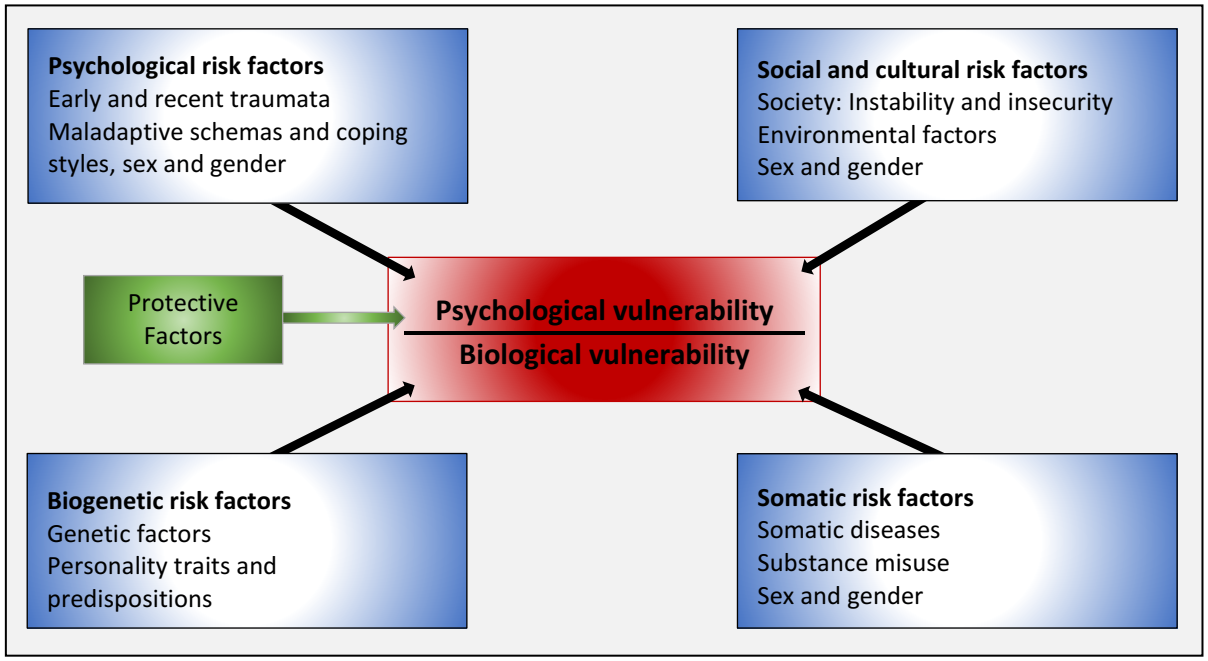

Figure 1: Psychobiological vulnerability for depression - adapted version from Schotte et al. (44)

The development of a DD is caused by an interaction of all three biological (e.g., genetic risks), psychological (personality traits like Neuroticism), and social factors (early childhood adversity and stressful life events) that determine vulnerability for DD (45, 44).

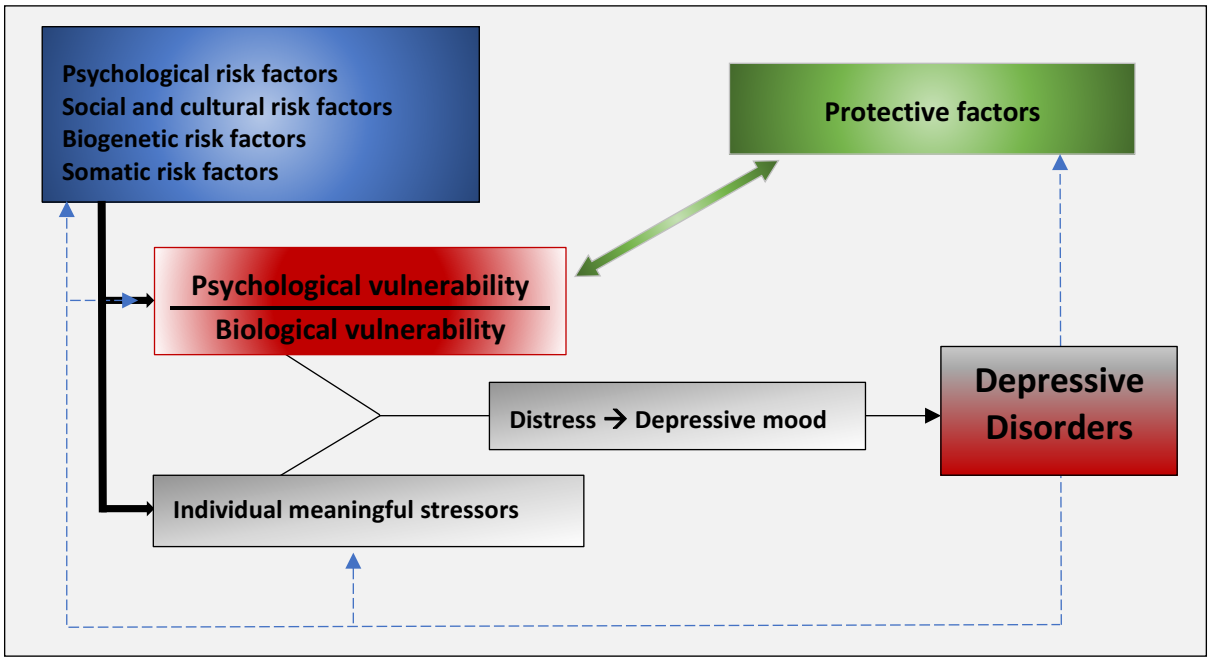

Figure 2: The diathesis–stress model for depression - adapted version from Schotte et al. (44)

Resent research demonstrates that ovarian hormone fluctuation can modulate women´s susceptibility to stress as well as their inflammatory activity and reactivity, altering brain structure and function, leading to a higher risk of developing an inflammation-related mood disorder in women (46). This is the case especially for women, with a predisposition of a DD or for women passing through a hormonal transition period (e.g., menopause, postpartum) (47, 46). DDs have been found to be heritable. Twin studies suggest that if one parent suffers from a DD, there is a 30%-40% chance that their child will suffer from this disease as well (48, 49). The genetic factor is divided into two aspects. On the one hand, personality traits, such as avoidance of harm, anxiousness, and pessimism can be heritable and individuals who have a strong inclination to one or more of these traits are at a higher risk of developing a DD (50). On the other hand, chromosomal regions with a connection to DDs have been found in multiple studies, and some have been replicated; however, no definite chromosomal region has been identified to be related to DD (42, 48, 13). The genetic factors contribute to the vulnerability of suffering from a DD, which can either be reinforced through biological, psychological, or social determinants, like stressful life events or stressful living conditions, or lowered by beneficial determents (51, 49). Few studies investigated sex differences in the heritability of DD — additionally the majority of preclinical research investigated exclusively male subjects (52). A very recent genetic study was able to identify five genetic markers associated with a higher risk of developing depressive disorders in women (53).

The monoamine-deficiency hypothesis

An example for the interaction of biological, psychological, and social factors is the monoamine-deficiency hypothesis. Monoamine oxidase A is an enzyme that metabolizes certain monoamines, like norepinephrine, dopamine, and serotonin (54). The hypothesis was developed as a consequence of the discovery of early antidepressants. These early antidepressants blocked the reuptake of serotonin and norepinephrine by the presynaptic neuron or inhibited the monoamine oxidase and had a positive effect on depressive symptoms. It led to the hypothesis that patients with a DD suffer from a monoamine deficiency (42). Monoamines are involved in various important processes such as mood, motivation, sleep, hunger, sex drive, and gratification loops, which are known to be affected in DD. Nevertheless, to this day it has not been sufficiently understood what role the monoaminergic systems, especially the serotonergic and dopaminergic system, play in the context of DD (55). Studies measuring the

serotonin and norepinephrine levels in plasma, urine, or cerebrospinal fluid fail to identify the deficiency in depressed individuals. This lack of proof of the monoamine deficiency has not been explained yet (42). However, a positron-emission tomographic study found that a subgroup of depressed patients showed a 30% increase of the enzyme tryptophan hydroxylase 2 (TPH-2) in the brain. The TPH-2 enzyme can only be found in the brain. This could be a reason why studies that looked at total enzyme activity of monoamines (body and brain) have not found differences (56). Further research is needed in this field. Sex differences in biological markers have been identified. There are differences in the monoaminergic system as well as the immune system and in the neuroplasticity of the brain (57). Women with a DD have been found to have a higher S100 calcium-binding protein, α-[11C]methyl-L-tryptophan brain trapping constant, higher Interleukin 6 and leptin levels, and lower serotonin receptor 1A and free triiodothyronine levels. Men have a higher reeducation in gamma-aminobutyric acid- and brain-derived neurotrophic factor (BDNF)-related genes. A positive correlation between the severity of symptoms and BDNF, tumor necrosis factor-α, C-reactive protein, and interleukin-1b was found only in women with a DD (57)

Stress, the hypothalamic–pituitary–adrenal (HPA) axis, and growth factors

Another important player in the complex interaction of biological, psychological, and social factors leading to DD is stress and its effect on the HPA. If an individual suffers from stress caused by biological, psychological, and / or social factors, the hypothalamus releases the corticotropin-releasing hormone (CRH). This results in a secretion of corticotropin into the blood and a stimulation of corticotropin receptors in the adrenal cortex, which then releases cortisol into the blood. Cortisol and CRH are suspected to be associated with depressive symptoms. Patients suffering from a DD often have elevated levels of both cortisol and CRH, as well as individuals with a history of sexual or physical abuse as children (58). Evidence suggests that sex hormones have an effect on the limbic brain and the regulation of HPA axis function. This could contribute to the dysregulation that can be found in patients with DD and could explain some of the sex differences in prevalence of DD (59). Additionally, women are more vulnerable to suffering from stressful life events and their effects (see 1.2.1.) and this could explain the higher risk of first onset depression in females (60).

An increase of monoamines in the synapses can reverse some of the long-term effects of stress by altering the hypothalamic-pituitary-adrenal axis. This could explain the positive effect

of antidepressants. Hence antidepressants do not elevate the mood directly but reduce the effects of stress caused by negative emotion or a negative life event (61). Numerous studies have been performed to pinpoint the developing factors of depression and, as mentioned above, there seems to be no simple answer. Multiple genetic, biological, and environmental factors and their influences on each other are involved.

1.3 Sex differences in essential variables associated with DD

An episode of a DD feels different to everyone. However, women as a whole seem to experience this mental disorder differently than men. Studies have shown that females tend to report more symptoms, particularly in self-ratings, which do not always coincide with clinical observations (32, 62–64). Furthermore, there is evidence that females remember depressive episodes better than men who tend to forget them (64). The scientific goal of this thesis is to look at central variables (biological, psychological, social) associated with DD and compare these aspects between women and men. As psychological, social and biological factors are involved in the development of DD as well as in the process of treating / recovering from a DD, all of these factors should be given attention in studying the gender gap in DD. The results could be used for treatment planning to provide better, individualized, and specialized treatments for men and women.

1.3.1 Sex difference in psychological factors

Coping strategies

Coping is defined as a psychological operation applied by an individual to manage the demands of a stressful event or situation and can be conscious or unconscious (65). Coping strategies are cognitive, emotional, behavioral, and physiological processes that are employed in a stressful situation to ease an individual's demand overload (65). The mostly synonymously used term "coping style" refers to an intra-individual stable coping behavior used throughout various situations (66). Thus, there is a tendency to apply similar coping strategies across different lifetime events, which could be considered an invariable characteristic determined through psychological testing (67). Stress coping strategies are identified in the context of Janke and Erdmann's (2002) stress coping strategies questionnaire SVF78 (see methods), therefore this term is considered to be adequate for this work. There is a further distinction between active and passive coping strategies (68), or between strategies leading to an increase of stress

(negative coping strategies) and strategies leading to a decrease of stress (positive coping strategies (69). Figure 3 describes the different positive and negative stress coping strategies as postulated by Janke and obtained by the SVF 78 (67).

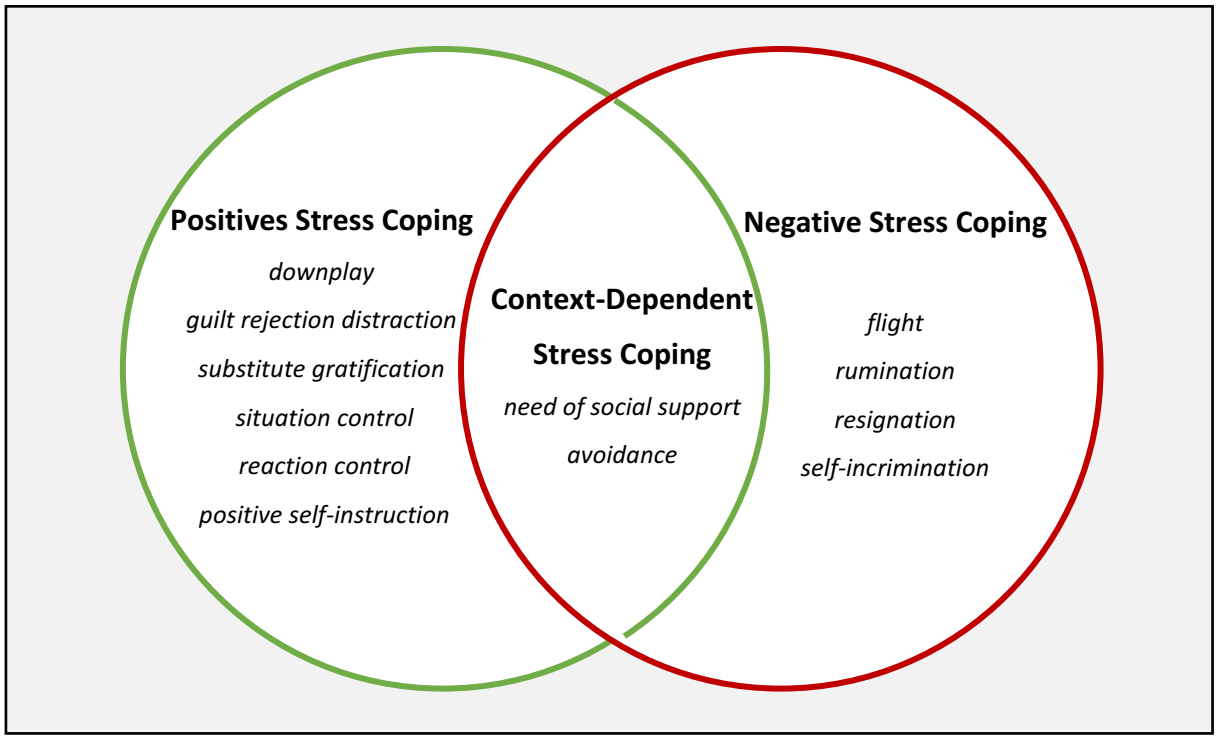

Figure 3: Classification of stress coping strategies (67) – generated by the author

Multiple studies have shown sex differences in the usage of coping strategies (70). From an early age, the social environments for boys and girls diverge. Boys are confronted with more active toys, like automobiles, war toys, Legos, and the like while girls are given more passive toys to play with like dolls, Barbies, ponies, etc. Boys are often raised to be mentally tough and girls to be passive and to internalize problems (24). Therefore, by even their earliest years, girls often develop a less active coping style (64, 24). Furthermore, women are physically and sexually abused more frequently than men (71–73).Victims of physical and / or sexual abuse often show lower self-esteem, more hopelessness, more depressive symptoms, and an external locus of control compared to individuals with no adverse childhood experiences (74). As a result of their traumatic experience, women often form unhealthy coping styles (75). Coping styles are essential when dealing with stressful life events. Stressful life events are defined as strong stimuli, like the loss of a loved one, marriage, child birth, trauma or the like, which can adversely affect someone‘s stress levels and thereby impact the rest of their life. Stressful life

events are associated with the etiology of various psychological and somatic diseases (76). Women report enduring more stressful life events than men. (60). A study showed that women are more likely than men to suffer from anxiety and anxiety disorders after a stressful life event (77). One reason for this difference appears to be that women mainly have intimate relationships with family or friends as a source of self-esteem and men have broader sources of self-esteem (work, hobbies, sports, friends, family) and use more active coping mechanisms. Therefore, women could be more vulnerable to suffering after a stressful life event if their main source of self-esteem is in jeopardy. In line with this, marriage is found to be a protective factor against depression in men while it can be a promoting factor for depression in women (21). A further reason why women report more stressful life events could be that they are more sensitive to life events (70). Women do not only suffer from life events more often and strongly. They also seem to be more affected by the life events of others in comparison to men. Women who care for children seem to be especially susceptible to painful life events, and are more likely to develop depressive symptoms as a reaction. This is referred to as the "Cost of caring" (78, 21). This could lead to the assumption that men do not experience empathy as strongly as women. There are various studies finding men to be less empathetic, however, it needs to be taken into account that sex-related differences in empathy mainly appear in studies using self-reported questionnaires and not objective measures (79, 21). It is not clear if there really is a sex difference in empathy or if it is caused by gender-role stereotypes. Nevertheless, men seem to have a more active response to negative life events and resulting moods (e.g., substance use, violent behavior) compared to the less active and more ruminative approach of women (rumination, self-blaming). This response is not affected by the initial source of the negative mood state, which may be psychological or biological (80, 25).

Parker and Brotchie also found that women tend to have a more internalized coping style while men have a more externalized one. A representative example for an internalized coping style is the coping strategy of rumination. Rumination appears to occur more often in women and is a strong predictor for the onset of a DD (81, 25). The difference in coping styles is displayed in the psychological comorbidities from which depressed female and male patients suffer. Multiple studies found a higher prevalence of anxiety and eating disorders in depressed women compared to their male counterparts (82–85). Men show a higher lifetime prevalence of substance dependence and abuse (86). Men seem to choose dampening strategies, such as alcohol and drug abuse more often than women to cope with stressful situations (87, 82, 84,

25). In addition, they have a higher prevalence of antisocial personality disorder and impulse control disorders. A study group analyzing 43.093 individuals found that women in general tend to suffer from internalizing disorders like anxiety and mood disorders, and men more often suffer from externalizing disorders like substance abuse and antisocial personality disorder (82, 86).

Big Five personality traits

There is a scientific consensus about five basic dimensions of personality traits, referred to as the "Big Five," which are stable over time (88). These broad personality traits are Openness to new Ideas, Conscientiousness, Extraversion, Neuroticism, and Agreeableness (89). The Big Five model is one of the most recognized approaches to measuring differences in personality (90). Multiple studies found sex-related differences in the Big Five personality traits, which vary across countries (91–95). Some studies found that women score higher on all five personality traits (93). A meta-analysis from Costa (94) and colleagues found that women score higher on Agreeableness, Neuroticism, and certain facets of Extraversion (warmth, gregariousness, positive emotions), and Openness (to feelings, aesthetics, and actions), whereas men were higher in a sub-facet of Extraversion (assertiveness and excitement seeking) and Openness (to ideas). In line with that, a study investigating a sample of 17.637 healthy subjects found women reporting higher levels of Extraversion, Agreeableness, Neuroticism, and Conscientiousness. No differences were found concerning Openness (96).

Research on the association between the Big Five personality traits and DD showed that low Extraversion, low Conscientiousness, and high Neuroticism are highly related to depressive symptoms and can be found in patients with DD (97). Neuroticism especially appears to be a crucial developmental factor for DD (85, 77). Neuroticism could be defined as an emotional responsiveness style defined by a down-regulated HPA-axis, a high brain activation response to negative stimuli, a high stress responsiveness, a high tendency towards harm avoidance, and an autonomic lability. Gonadal hormone changes in women can lead to limbic system hyper activation in response to negative stressors and may therefore cause a higher vulnerability to stress (98). A higher responsiveness to negative events could have been an evolutionary advantage for women. It could benefit their survival and the survival of the ones in their care (e.g., small children) if they were able to detect dangerous situations or invaders faster. This was not as important for men who were not responsible for the upbringing and supervision of

the children (98, 97). Research on sex differences in the Big Five personality traits of patients with DD has not been conducted to the knowledge of the author.

These findings lead to the following scientific questions:

Do women with DD use negative coping styles significantly more often than man, and do men with DD more often use positive coping styles? If this is the case, it would have important implications for the treatment of female and male depression.

Furthermore, the scientific question arises: do women with a depressive disorder show significantly higher levels of the Big Five personality traits in comparison to men when they have a similar severity of depression?

1.3.2 Sex differences in biological factors

Somatic symptoms

Multiple studies failed to find different somatic symptom patterns in depressed female vs. male patients (64). Some studies found that sleep changes (62, 99, 63, 84, 86), changes in eating habits and weight (62, 63, 85, 86), as well as anxiety (99, 84, 85) and somatization (62, 99, 84) are more common in women with DD. In line with these findings, sex-related differences are especially dominant in atypical depression, which is characterized by increased appetite, hyperphagia and hypersomnia, and is more often found in female patients (64). In atypical depression these somatic conditions seem to be more homeostatic features rather than symptoms of the disorder (100, 64).

Additionally, chronical physiological conditions like cardiovascular diseases (CVD) and metabolic diseases are highly associated with DD (14–16). Affective disorders and chronical diseases facilitate each other, and there is often no clear answer as to what developed first, the mood disorder or the long-term illness. A study found that the following medical conditions are strongly associated with DD: back pain, gastrointestinal problems, genitourinary and musculoskeletal conditions, chronic fatigue syndrome, fibromyalgia, and metabolic disorders (101).

Little research was carried out concerning the topic of sex-related differences in somatic comorbidities in DD. It was ascertained that depressed women more often have a thyroid dysfunction (15, 102) and suffer from migraine headaches more frequently than men. A ratio

of 5:1 was reported. (103). Vice versa, men suffer from cardiovascular diseases more often compared to women (104, 14–16).The lack of research in this field calls for further investigation on sex-related comorbidity in depression, because it can lead to a better treatment of the DD and its comorbidities.

These findings lead to the following scientific questions:

Do women with DD show significantly different rates of somatic comorbidities in comparison to men with DD?

Inflammation and the kynurenine (Kyn) and tryptophane (Trp) breakdown

In the last decade the international research community has developed an increased interest in the topic of depression and inflammation and the related concept of the Kyn and Trp breakdown. In various studies a strong association between DD and systemic inflammation has been found (for an overview see (105)). Inflammation is connected to monoamine regulation. Inflammatory processes can increase the levels of interferon-gamma inducing indoleamine 2,3-dioxygenase-1 (IDO), which leads Trp down the Kyn pathways rather than the pathway to serotonin and melatonin synthesis. This process has been associated with a decreased level of central serotonin and with the development of DD (106–111). Alterations in neuroregulatory Kyn pathway products and in the ratio of these products (Kyn/Trp ratio) can change glial-neuronal networks, which may lead to a higher susceptibility of the brain to developing a mood disorder (110, 112). The Kyn/Trp ratio serves as a proxy measure of the activity of IDO (113). A study on sex differences in healthy adults found a higher concentration of free plasma Trp and a higher total Trp in women compared to men. No differences were found with Kyn (114). There is evidence that inflammation is a stronger mediator of depression in women compared to men (43). Studies investigating the differences in Kyn, Trp, and Kyn/Trp ratio between women and men with DD have been scarce; however, there are animal studies. A study investigating flinders sensitive line rats (genetic rat model of depression) found alteration in the tryptophan metabolism only in females (115). A study (116) investigating sex differences in the Trp metabolism in anxiety disorders found that in women an immune activation more often affects the IDO compared to men, which can lead to an increase of anxiety. A very recent study found that depressed females have higher TPH enzymes (TPH-1 and TPH-2) compared to healthy females. This difference was not found in male individuals with a DD (117). Further

investigation is needed to clarify the complex mechanisms of the tryptophan breakdown and its association to depressive symptoms.

These findings lead to the following scientific questions: Do women with a DD show a significantly higher Kyn/Trp ratio in comparison to men with a DD? Given that the data is available, it is further interesting to question whether women with a DD show different changes of Kyn, Trp, or the Kyn/Trp ratio after a six-week rehabilitation program (see also 1.4) in comparison to men with a DD.

1.4 Sex differences in treatment of DD

There have been only a few studies on the effect of the patient's sex on the treatment of DD. Those few studies were not able to provide consistent results on the topic.

In general, women tend to seek help earlier and more frequently than men (24, 13). In a web-based survey the study authors found that women described cognitive behavioral therapy and counselling as more effective than other treatment methods. Men did not report any differences (118). The authors suggested that the findings could indicate that women more readily form a treatment alliance, while men are more guarded and defensive about their mental state and treatment. In line with this, women often seek help at an earlier stage and they consult professionals more frequently (32, 64). The sex of the health care professional as well as the sex of the patient might significantly influence the success of the treatment. Male professionals tended to show less eye contact, appear to be less caring, more often suggested solutions before hearing the patient out, and were more likely to prescribe drugs as monotherapy (64). Female patients wished to return to female professionals more often than to their male colleagues (64).

Antidepressant medication

No consensus has been found as to whether the effectiveness of antidepressants is influenced by sex (119). Few studies have found sex-related differences. Monoamine oxidase (MAO) and selective serotonin reuptake inhibitors (SSRIs) were described to be more effective in women (83, 120), although the effect diminishes once women enter menopause (83). Men have been found to better respond to tricyclic antidepressants (121, 83). Nevertheless, a large study on 1,746 patients failed to find any sex-related differences in treatment response to SSRI fluoxetine

or tricyclic antidepressants. However, the study authors found a better response to MAO inhibitors in women compared to men (122). Several meta-analyses and studies were not able to detect differences in terms of drug response when comparing women to men (123, 119, 124, 125). Parker et al. concluded in a meta-analysis that differences in response to antidepressant medication predominantly underline biological differences rather than sex-related factors (126). There is evidence that women with DD receive a different psychopharmacological treatment than men with DD (127, 128). Furthermore, bupropion and mirtazapine were found to be prescribed more often to men in a recent study (129). Reasons for the differences in prescribed drugs are yet to be explained. Despite some studies existing on this topic, studies including a larger range of patients in which severity of depressive symptoms as well as age are controlled have not been conducted before. With this study the comparison of men and women, similar in age and in depressive symptomology, can bring valid insights into the topic.

These findings lead to the following scientific questions: Do women with DD show significantly different drug prescriptions than men?

Polypharmacy

Another important topic relating to the psychopharmacological treatment of DD is the number of drugs prescribed and the risk of polypharmacy. Polypharmacy as defined by the National Association of State Mental Health Program Directors is the intake of more than one drug for a patient's medical condition (130). The term suggests that the number of medications prescribed surpasses the number that is clinically indicated (131). Polypharmacy is associated with a higher risk of side effects, drug-to-drug interactions, and increased health costs (132). Nevertheless, poly-pharmacological treatment in mentally ill patients has become more and more common (133, 134). This trend appears to be based less on medical evidence or guidelines and more on subjective experiences (135). A detailed review shows that monotherapy in the treatment of psychiatric patients decreased in the last decades from 47.8% in 1980 to 19.6% in 2000. More recent data from 2006-2015 of patients with a DD (n =6.685) presented the prevalence of polypharmacy to be at 54%. As outlined by the authors, about half the cases of polypharmacy were justified by augmentation strategies (136). Polypharmacy is not only found in young and middle-aged adult patients but is especially common in the treatment of older patients (131). Looking at psychotropic polypharmacy, a Brazilian study found that 84.9% of women and 85.7% of men with psychiatric diseases took two or more psychotropic drugs (137).

There was an average number of 2.98 drugs per patient, with no difference between women and men. Nevertheless, evidence of sex-related differences in psychotropic polypharmacy remains sparse. No sex-related differences were found in two studies comparing single vs. multiple psychotropic drug use (132, 137). Interestingly, associated factors of psychotropic drug polypharmacy diverged between men and women. Women showed a correlation between multiple psychotropic drug intake and higher education, advanced age, and multiple chronic diseases. In men psychotropic polypharmacy was associated with lack of occupation, insomnia, white skin color, and a higher number of health problems (self-reported) (138). In another study, especially young patients and men in general were found to be at risk for psychotropic polypharmacy (135). Gulla et al. found older people, especially elderly women, to be more often effected by polypharmacy (139). A recent study by Seifert et al. found evidence of women taking four or more drugs more often compared to men (129). Again, there is a lack of studies that control for the severity of depression and age when comparing women with men. This study will provide a more accurate and valid picture of sex differences in polypharmacy in the treatment of DD.

These findings lead to the following scientific questions: Do women with DD show a significantly higher number of psychotropic medications in comparison to men with DD?

1.5 Psychiatric rehabilitation in Austria

Psychiatric rehabilitation is recommended for patients with a mental illness after acute psychiatric treatment or as a preventive measure in case of a less pronounced symptomatology. There are options for inpatient and outpatient settings available. In Austria, psychiatric rehabilitation in an inpatient setting is usually offered for a duration of six weeks. The focus of psychiatric rehabilitation programs, in contrast to acute curative psychiatric treatments, is mainly placed on long-term symptom management. Major goals are the improvement of the quality of life, development of social competences, the ability to participate in daily (work) life, the strengthening of cognitive abilities, and the prevention of rehospitalizations (140). According to Austrian social security guidelines, there are three basic requirements for patients with mental disorders to participate in psychiatric rehabilitation programs (140). First, the patient has to have a need for rehabilitation. This means that there should be a necessity to undergo a multimodal program after being in acute care in a hospital. Second, the patient needs

to be capable of participating in a rehabilitation program. The patient should be motivated and psychologically as well as physically resilient in order to successfully take part in the rehabilitation program. Third, the patient has to have a positive rehabilitation prognosis. This is the case if the patient has the potential to achieve predefined rehabilitation goals. To accomplish these rehabilitation goals, skills are developed during the psychiatric rehabilitation process to help the patient increase daily functioning, or a support network is implemented to – at least – maintain the person's present functioning level (141). The challenge of psychiatric rehabilitation is to provide both somatic and psychiatric care as well as vocational and social interventions. Psychiatric rehabilitation provides a predefined treatment plan for each patient that combines medical, psychiatric, psychological, and psycho-therapeutic treatment, occupational and physical therapy, and dietary counseling. All patients have similar levels and extent of therapy, therefore the treatment outcome of different patient groups (e.g., women vs. men) can easily be compared.

Although there is now a wide range of psychiatric rehabilitation facilities in Austria and Germany, evaluation studies examining the effects of such programs are still lacking. The lack of research in this field is caused by a broadly shared view that psychiatric rehabilitation is a second- or third-line treatment applied only if all other inventions have failed. Additionally, it was assumed that any mental health care professional (e.g., psychologist, psychotherapist, psychiatrist, psychiatric nurses) can carry out the intervention without receiving special training beforehand (142). Fortunately, this has been changing in recent years and the paradigms of psychiatric rehabilitation have been better defined and consolidated by evidence-based research (143, 142). Nevertheless, the implementation of interventions supported by scientific evidence remains a major challenge of psychiatric rehabilitation (144). For many years, high-income European countries invested in too-expensive services which were not evidence-based, nor recovery- or personalized-care-oriented (145). On these grounds it is not surprising that studies comparing the treatment response of women and men attending a psychiatric rehabilitation clinic are nearly nonexistent (16, 146). The psychiatric rehabilitation clinic where this study took place has a strong focus on the improvement of stress management and stress resilience as well as the reduction of oxidative stress in the body. These goals are meant to be achieved by an extensive sports program, a healthy diet, and specialized psychotherapeutic groups like mindfulness, burnout prevention, anxiety coping, and relaxation groups. The staff consists of

well-trained sports scientists, physical therapists, diet consultants, psychotherapists, psychologists, psychiatrists, and general practitioners.

These findings lead to the following scientific questions:

Do women, compared to men, show different changes in coping styles or inflammatory bio-markers (Kyn, Trp, Kyn/Trp ratio) during a 6 week-rehabilitation program?

1.6 Study design

The study was divided into two different parts. Firstly, sex-related differences of women and men with DD were compared in a cross-sectional observational study design. The measurements took place at the beginning of a six-week rehabilitation program. Secondly, changes during the rehabilitation program and the potential effect of the sex of the patients on these changes were investigated in a longitudinal study design. The two measurement points were located at the beginning (T1) and the end of the rehabilitation program (T2) and there was an average time period of five weeks between these two time points (see Figure 4). The study focused on three main study objectives.

Objective I: In order to answer the question of whether women with DD differ from men with DD on certain variables (*coping styles and Big Five personality traits, somatic comorbidity, inflammatory bio-markers, and medication*), the variables were compared between women and men at the first measurement point (T1).

Objective II: To investigate if there were differences in changes after a six-week rehabilitation program between men and women with a DD the relevant variables (see above) from T1 to T2 were compared between women and men.

Objective III: To investigate if coping styles or the Big Five personality traits can predict the severity of depressive symptoms (BDI-II sum score), a regression analysis was performed. This was done separately for women and men to explore if the regression weights differ between women and men.

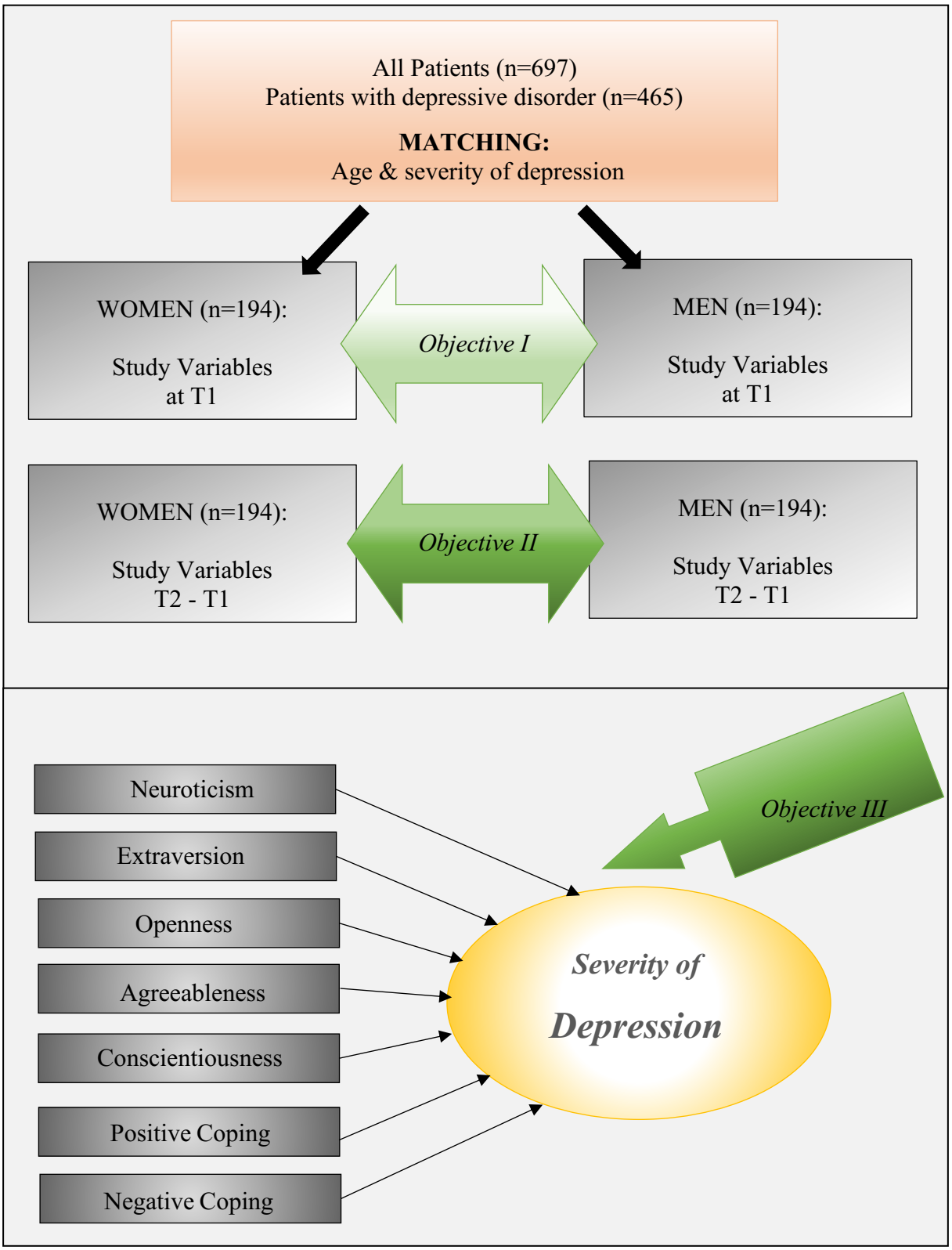

Figure 4: Overview of the study design: Objective I=differences between women and men with DD in key variables; Objective II=differences in rehab changes between women and men with DD in key variables; Objective III=predictors of severity of depression – are there sex differences?

2 Objectives and Hypotheses

2.1 Aim of the Study

The aim of this study was to further investigate sex-related differences between males and females suffering from DD concerning (1) psychological variables (coping styles and Big Five personality traits), (3) somatic comorbidities, (4) inflammatory bio-markers, and (5) pharmacological treatment. In addition, the aim was to test if there are sex-related differences in the changes in those variables during a six-week rehabilitation program.

Issues / objectives:

I. What distinguishes women and men with DD? Are there differences between women and men with DD in:
    1. Psychological variables (coping strategies and Big Five personality traits)
    2. Somatic comorbidity and inflammatory bio-markers (Trp, Kyn, Kyn/Trp ratio)
    3. Treatment (medication)

II. Are there differences in the changes in coping styles and inflammatory bio-markers during a six-week psychiatric rehabilitation program between men and women?
    4. Women vs. men with a DD: which parameters (psychological and biological) change during the rehabilitation program?

II. Determinants of Recovery: Can the coping styles or the Big Five personality traits predict the severity of depressive symptoms?
    5. Which determinants are associated most strongly with the severity of depressive symptoms?
    6. Are the regression weights different in women and men? Are there sex-related differences?

2.2 Hypotheses

2.2.1 Null Hypothesis

I. There are no differences between women and men with a DD in the examined psychological, physiological, and treatment variables.

II. There is no difference in the changes during the rehabilitation program between women and men with a DD.

III. There are no differences in determinants for the severity of depression in women vs. men with a DD.

2.2.2 Main Hypothesis (H)

AD objective I

1. Coping styles and Big Five personality traits

Are there differences between women and men with DD undergoing psychiatric rehabilitation treatment at time of admission (T1) in their coping strategies or their Big Five personality traits?

H1a: Women with a DD use negative coping strategies significantly more often than men.

H1b: Men with a DD use positive coping strategies significantly more often than women.

H1c: Women with a DD show significantly higher values of all Big Five personality traits in comparison to men.

2. Somatic comorbidity and inflammatory bio-markers

Are there differences between women and men with DD undergoing psychiatric rehabilitation treatment at T1 (time of admission) concerning their somatic illnesses and their Trp and Kyn levels or Kyn/Trp ratio?

H2a: Women with depressive disorders show significantly higher rates of somatic comorbidities in comparison to men.

H2b: Women with depressive disorders show significantly different Kyn and Trp level or Kyn/Trp ratio in comparison to men.

3. Treatment history and medication

Are there differences between women and men with DD undergoing psychiatric rehabilitation treatment at T1 (time of admission) in their treatment history or their current medication (kind and number of drug)?

H3a: Women with depressive disorders show significantly different drug prescriptions than men.

H3b: Women with depressive disorders show use of a significantly higher number of psychotropic drugs in comparison to men.

AD objective II

Do women with DD compared to men with DD show significantly different changes in their coping strategies or their Kyn level, Trp level, or Kyn/Trp ratio between T1 (time of admission) and T2 (discharge) of the rehabilitation program?

H4a: Women with depressive disorders show significantly different changes in their coping styles compared to men after a six-week rehabilitation program.

H4b: Women with depressive disorders show significantly different changes in Trp and Kyn levels and in the Kyn/Trp ratio in comparison to men after a sxi-week rehabilitation program.

AD objective III

III. Can the coping styles or the Big Five personality traits predict the severity of depressive symptoms? Which determinants are associated most strongly to the severity of depression? Are the regression weights different in women and men?

3 Material and methods

3.1 Sample & location

The study subjects were recruited from a psychiatric rehabilitation clinic in Upper Austria from April 2015 to March 2016. The recruitment and data collection were conducted within the main study project ("The Neurobiological Foundation of Burnout Syndrome").

The rehabilitation clinic is a hospital inpatient center for psychiatric rehabilitation specialized in psychiatric conditions, such as affective disorders, anxiety disorders, and personality disorders. All patients were governmental employees and completed a six-week rehabilitation program, consisting of psychological, physical, and medical therapy, as well as ergo-therapy and dietary treatment. At admission and discharge there was a thorough examination procedure, assessing the physiological and psychological health status.

3.2 Ethics vote

The study protocol was approved by the ethics committee of Linz and Graz (EK Number, E-24-14). All procedures were in accordance with the standards of the Helsinki declaration.

3.3 Inclusion and exclusion criteria

All patients between the ages of 18 and 75 years who were treated at the rehabilitation clinic were included in the study if they gave written informed consent.
The following exclusion criteria were defined:

- Patient refused to participate
- ICD 10 F2x.x - diagnose: schizophrenia, schizotypal, and delusional disorders
- Current organic brain disease (epilepsy, brain tumor, insult, dementia, severe head trauma / brain surgery) or acute psychotic symptoms
- Moderate and severe mental retardation
- Doctor's discontinuation: A patient was excluded from the study if e.g., during the stay an acute severe mental illness occurred (e.g., severe depressive episode with suicidality, acute psychotic episode, etc.) or the patient did not feel able to participate further in the rehabilitation program. If the first measurement time had already been completed by

then and informed consent was not retained, data were included in the analysis. If it turned out that the patient was already suffering from an acute severe mental disorder at admission, the data were not included in the analysis.

3.4 Procedure

At time of arrival at the clinic all patients were informed of the opportunity to participate in the study and after giving their written informed consent they were included in the study. In case of refusal, there were neither advantages nor disadvantages for the patients. The examinations were included in the routine procedure of admission and discharge since examinations in general were needed for clinical diagnostics and therapy. Upon consent to participate, the study patients agreed that the data of the examinations could be used for study purposes as well. Every patient had the right to revoke his or her participation and thus the processing of the collected data at any time and without explanation. If desired by the patient, it was also possible that only certain parts of the study examinations were included, though no patient voiced this desire. T1 took place within the first three days upon admission and T2 was scheduled within the last week before discharge. During the testing phases break times were provided if needed and in case of discontinuation of the testing, it could be repeated or completed within 48 hours (T1 and T2). Upon discharge, the subjects received a detailed report (summary of the test results) as well as the possibility to discuss the results with a psychologist. See Figure 5 for an overview of the study protocol and interventions / treatments.

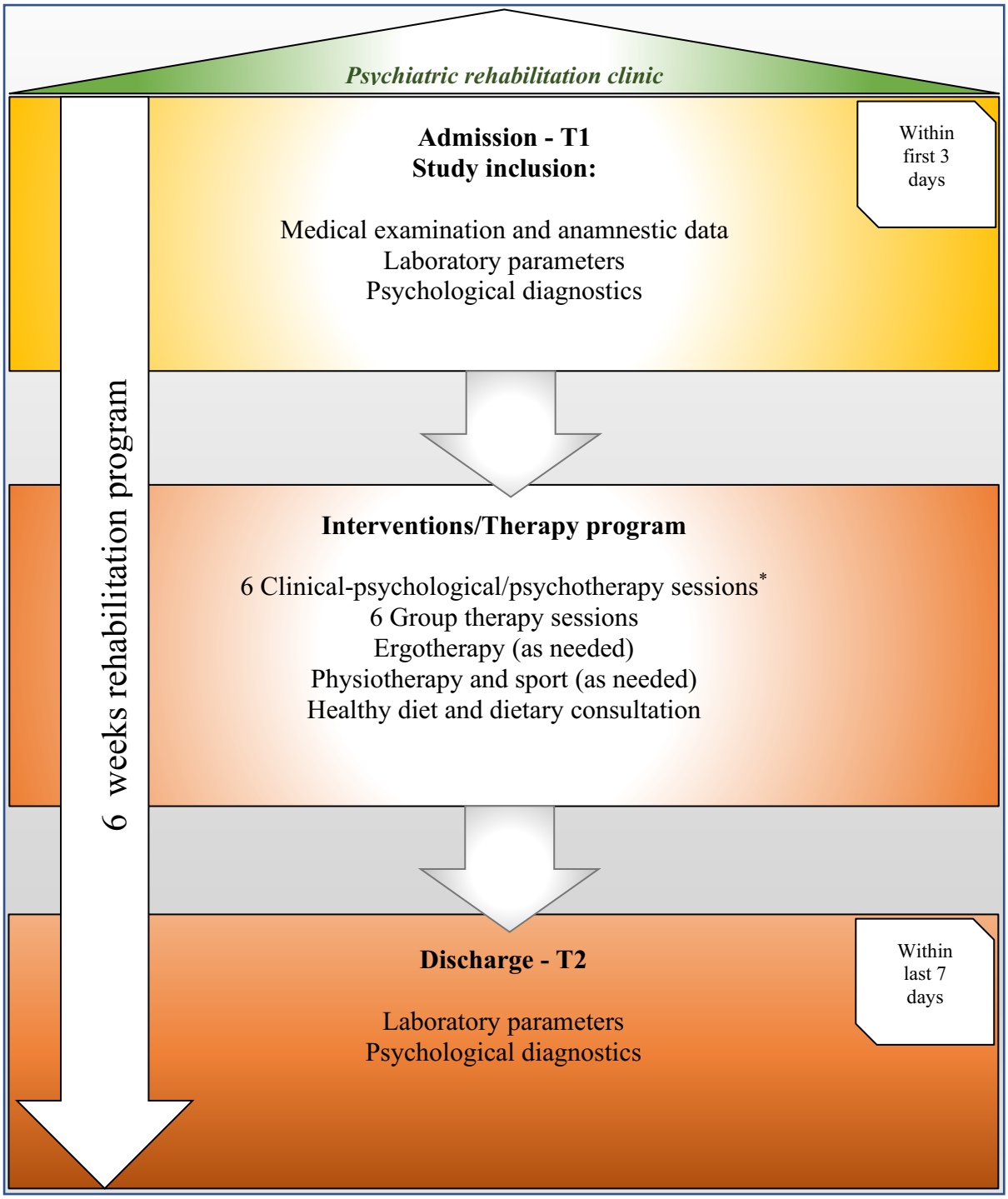

Figure 5: Overview of the study protocol and interventions; *Sessions were held either by clinical psychologists or psychotherapists

3.5 Obtained parameters – Study variables (see also Table 1)

3.5.1 Socio-demographic data

Socio-demographic data were collected by a questionnaire which had been created by the study team of the main study project ("The Neurobiological Foundation of Burnout Syndrome"). It was sent to the patients prior to admission to the rehabilitation program. The patients completed the questionnaire and either brought it with them at the beginning of the rehabilitation program or sent it by mail prior to their arrival. For this dissertation information about the sex, date of birth, education level (seven categories: no graduation, elementary / secondary school, polytechnic institute, junior high school, high school, [technical] college, university), and current occupation of the patients was used for further analysis.

3.5.2 Physical examination and anthropometry

The consent forms were signed in the context of the medical admission (75 min), in which the study was introduced and elucidated by a practitioner. A physical and clinical examination was performed and a blood sample was drawn. Current diseases and history of diseases as well as a current medication record were requested, and blood pressure was measured with the medical device *Medicus plus* by *Boso*. This examination was performed during the first three days of the rehabilitation program (T1). Body mass index (=BMI [weight / height^2]) was recorded by a nurse using a *Seca mBCA 515* medically valid bio impedance scale for the weight and a measuring tape, which was fixed on the wall to determine the height of the study subjects (5 min).

In the first week following admission an ergometry was carried out by a sport scientist on an ergometry bike (*911 BP* by *Ergosana*) after trained nursing staff had properly placed the electrocardiogram (*ECG ergometer C2 200 touch by Schiller*) to measure heart rate at rest and at performance peak. This process was part of the routine program of the psychiatric rehabilitation clinic that every patient, independent of their study participation status, underwent.

3.5.3 Laboratory parameters

To measure serum inflammatory markers a fasting blood sample was drawn on the morning of the second or third day following arrival in the morning between 8:00 am and 9:30 (T1) and

within the last seven days before discharge (T2). The total quantity of blood withdrawn was a maximum of 100 ml. The samples were stored at -80 °C until defrosted for the final biological assays. A high-performance liquid chromatography was used to determine free serum concentration of Trp and Kyn. This process is described in detail in (147). By dividing the Kyn free serum concentration by the Trp free serum concentration, the Kyn/Trp ratio was calculated, which serves as an IDO proxy, since the Kyn/Trp ratio is an index of Trp breakdown. Identical chromatographic conditions (column) and standards were used to run the samples.

3.5.4 Psychological diagnostic

The clinical diagnostic, stress coping diagnostic, and personality diagnostic were performed on the computer in the diagnostic room supervised by clinical psychologists (duration around 90 minutes). This was standard procedure for every patient in the rehabilitation clinic independent of their participation of the study. Several questionnaires were handed out to the patients and had to be filled out and returned within 24 hours. The questionnaires were thereafter evaluated by a clinical psychologist. The questionnaires that were used for this dissertation are described in detail below.

Clinical diagnostic

- The Beck Depressions Inventory II (BDI II) (148) assesses the severity of depressive symptoms on the basis of 21 items. It is a self-report measurement. The items include questions about mood, sleep, eating habits, sex drive, and suicidal tendencies.

- The Hamilton Depression Scale (HAMD) (149) is an external assessment to determine the severity of depression based on 21 symptoms or symptom complexes.

Stress coping

- The Stress Management Questionnaire (SVF-78) allows the assessment of the usage of different coping or processing strategies in stressful situations. As a result of the questionnaire the usage frequency of the following twelve coping strategies can be determined: downplay, guilt rejection, distraction, substitute gratification, situation control, reaction control, positive self-instruction, need of social support, avoidance, flight, rumination, resignation, and self-incrimination. Five global scales are calculated as well: use of defense/devaluation strategies, distraction strategies, control strategies, as well as total positive strategies and negative strategies (67).

Personality testing

- The Big Five Inventory - German version (BFI-10) is a short inventory consisting of ten items to capture the Big Five personality variables: *Neuroticism, Extraversion, Openness (to ideas), Agreeableness,* and *Conscientiousness.* Each personality trait is measured with two items (150). Since personality traits are anticipated to be stable over time, the BFI-10 was only applied at T1.

Table 1: Overview of obtained parameters (study variables)

	Parameters	**Time**
Socio-demographic data	Date of birth	T1
	Sex	T1
	Education level *Categories: no graduation, elementary / secondary school, polytechnic institute, junior high school, high school, [technical] college, university)*	T1
	Occupation	T1
Physical examination & anthropometry	Current somatic illnesses	T1
	Current psychiatric medication	T1
	BMI (weight/height^2)	T1
	Systolic and diastolic blood pressure	T1
	Heart rate in rest and at peak (ergometry)	T1
Laboratory parameters	Tryptophan (Blood serum analysis):	T1 and T2
	Kynurenine (Blood serum analysis)	T1 and T2
	Kynurenine-tryptophan ratio (kynurenine/tryptophan)	T1 and T2
Psychological diagnostics	BDI-II: Depression score (self-report)	T1 and T2
	HAMD: Depression score (external rating)	T1 and T2
	SVF-78 – Subscales: *downplay, guilt rejection, distraction, substitute gratification, situation control, reaction control, positive self-instruction, need of social support, avoidance, flight, rumination, resignation, self-incrimination*	T1 and T2
	BFI-10 – Subscales: *Neuroticism, Extraversion, Openness (to ideas), Agreeableness* and *Conscientiousness*	T1

BMI=Body mass index
BDI-II=Beck Depression Inventory Version II
HAMD=Hamilton Depression Scale
SVF-78=Stress Coping Questionnaire (German: Stressverarbeitungsfragebogen)
BFI-10=Big Five Personality Traits Inventory
T1=time of admission, T2=time of discharge

3.5.5 Pseudonymization of the data

The participants' code served as an encryption of the data, and was only accessible for selected study team members in a file with restricted access. In all other files, the codes and the names were always kept separate from each other. The database is stored in a secure directory and access to the database is restricted to study team members only.

3.6 Sample selection and matching

3.6.1 Psychiatric diagnosis

After collection and analysis of anamnesis and psychological test results the diagnosis was determined by an interdisciplinary team of a psychiatrist, a general practitioner, a psychologist, and a nurse. Psychiatric diagnoses were made according to the ICD-10 diagnosis manual as follows:

- F00-F09 Organic, including symptomatic, mental disorders
- F10-F19 Mental and behavioral disorders due to psychoactive substance use
- F20-F29 Schizophrenia, schizotypal, and delusional disorders
- F30-F39 Mood [affective] disorders
- F40-F48 Neurotic, stress-related, and somatoform disorders
- F50-F59 Behavioral syndromes associated with physiological disturbances and physical factors
- F60-F69 Disorders of adult personality and behavior
- F70-F79 Mental retardation
- F80-F89 Disorders of psychological development
- F90-F98 Behavioral and emotional disorders with onset usually occurring in childhood and adolescence
- F99-F99 Unspecified mental disorder
- Z73.0 Problems related to life-management difficulty, e.g., burnout syndrome.

3.6.2 Selection and matching process

On the whole data from 697 patients were collected. From this pool of patients, patients with F33.x and F32.x diagnoses were selected since the study focused on sex differences in patients

with a DD. According to this selection, 465 patients of the sample were diagnosed with a depressive disorder (F33 or F32). 200 out of the 465 patients were male and 265 were female. In order to ensure a similar severity of depressive symptoms and a similar age in both groups, women and men were matched based on their scores in the Beck´s Depression Inventory (BDI-II) and their age. The matching procedure was carried out manually by using the program Microsoft Excel 2016. As a result, differences between groups – if present – could be attributed to sex and not to the severity of depressive symptoms or age. Additionally, through this process an equal sample size of females and males was achieved. This process resulted in 194 female and 194 male participants.

3.7 Statistical analysis

For the statistical analysis the statistic program IPM SPSS Statistics 26 was used. Depending on scale and distribution, T-tests, chi-square tests, non-parametric tests (Kruskal-Wallis-Test, Kolmogorow-Smirnow-Test, Mann-Whitney-U-Test), or multivariate variance analyses (MANOVA) were used to test the hypotheses. Whenever multiple statistic tests that elevated the risk of a higher alpha error were calculated, the false discovery rate was used. The repetition effects were calculated using multivariate analyses of variances with repeated measures (fixed effects, main effects, and interactions: UV1 = sex, 2-fold). The multivariate analysis of variance (MANOVA) with repeated measures was performed to investigate changes during the six weeks of psychiatric rehabilitation. Additionally, the changes due to rehabilitation were compared between females and males. The assumptions for a MANOVA are the independence of the cases, the normal distribution of the residual (can be neglected, if case number is above 25), the equality of variances (Homoscedasticity), as well as the absence of multivariate outliers, linearity, absence of multicollinearity, and equality of covariance matrices. The requirements were met or the deviations were negligible.

A stepwise regression analysis was performed to investigate if coping styles or the Big Five personality traits can predict the severity of depressive symptoms at T1. To investigate sex-related differences, the regression analysis was administered separately for women and men. The assumptions of the regression analysis (linearity of regression coefficients, homoscedasticity, independence of errors, normality of error distribution, lack of multicollinearity) were met or the deviations were negligible.

4 Results

4.1 Sample description

After the matching procedure, the data of 388 patients (194 females) were analyzed. The mean age of the participants was 52.34 years with a standard deviation (SD) of 7.80 years (females: M=53.87; SD=7.44 / males: M=51.81; SD=8.14) and the mean body mass index (BMI) amounted to 27.17 (SD=5.06; females: M=27.00; SD=5.64 / males: M=27.34; SD=4.42). There was no significant difference between the average BMI of females and males ($t(382)=-0.64$, $p=.523$). The majority of patients were employed in public service (e.g., education, military, police, and government). The occupational fields of the participants are displayed in Table 2. The education level is displayed in Figure 6. There was a significant difference in the level of education between females and males (U=10629.5, p=.006). Women with DD showed a significantly higher education level compared to men with DD.

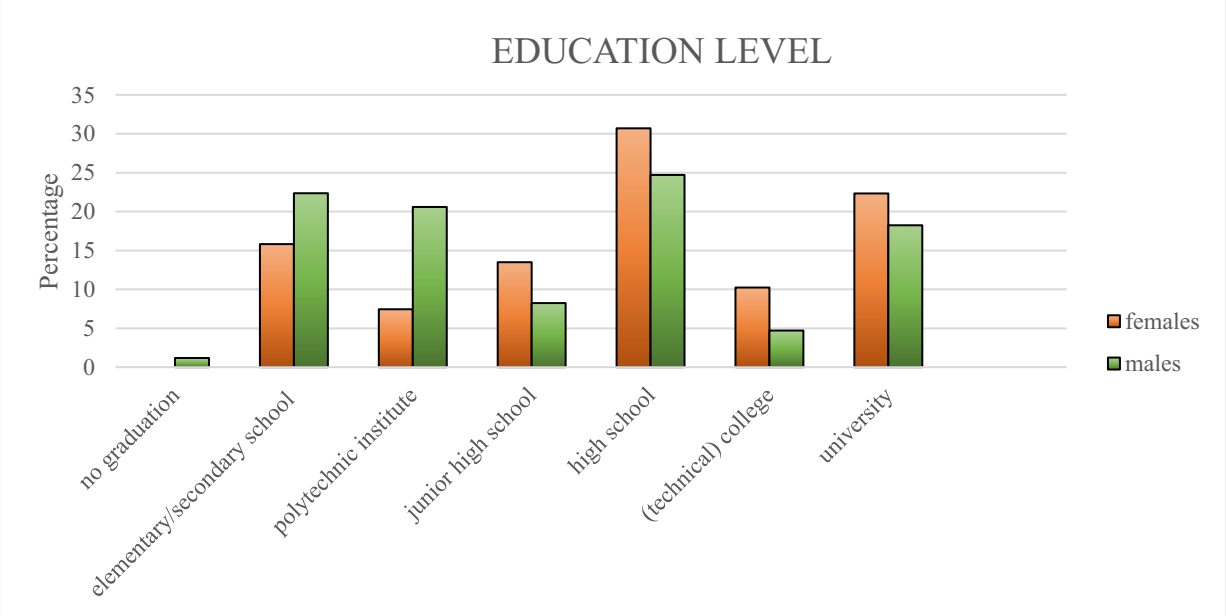

Figure 6: Distribution of education level between females and males

Table 2: Occupational fields of participants comparing females and males.

Field of occupation	Females % (n)	Males % (n)
Officialdom	20.1 (39)	26.8 (52)
Teaching	35.1 (68)	10.8 (21)
Police	3.6 (7)	12.9 (25)
Justice system	1.6 (3)	5.2 (10)
Postal system	2.6 (5)	6.2 (12)
Medical care	5.2 (10)	1.6 (3)
Craftsmanship	0	2.6 (5)
Trade/economy	4.6 (9)	3.6 (7)
Banking sector	1.6 (3)	1.6 (3)
Building trade	0	1.6 (3)
Employee	3.1 (6)	2.6 (5)
Child care	3.1 (6)	0
Army	0	4.1 (8)
Other*	8.2 (16)	15.0 (29)
Not specified	11.3 (22)	5.7 (11)

%=Percentage of females / males working in that field.

n= Number of females / males working in that field.

*other=homemaker, IT / technician, gastronomy, cleaning, mechanic, retirement, in training, social care

All patients were diagnosed with a DD and did not differ significantly in the HAMD Score (females: M=11.02; SD=6.35 /males: M=12.49; SD=7.36, Z=-1.789, p=.074), or the BDIII - score (females: M=20.25 SD=10.23 /males: M=20.08; SD=10.83; Z=-0.293, p=.770). A Mann-Whitney-U Test was performed since the variables HAMD score and BDI-II score were not normally distributed. Psychological comorbidities are displayed in the appendix Table 17.

4.2 Objective I – Sex differences in variables associated with depression

The main hypothesis of the study was that women with DD differ in several psychological, physiological, and treatment-related variables from men with DD.

4.2.1 Psychological variables

Coping style

In order to investigate the differences in coping styles, the subscales of the SVF-78 were compared between females and males. Females showed significantly higher scores in the subscales *substitute gratification, need of social support*, *rumination,* and *self-incrimination* and in the global scales *usage of distraction strategies* and *negative strategies*. The MANOVA showed that male participants had significantly higher scores in the subscales *downplay* and *blame rejection* and the global scale *usage of defense / devaluation strategies*. There were no significant sex-related differences in the subscales *distraction, situation control, reaction control, positive self-instruction, avoidance, flight, resignation* and the global scales *usage of control strategies* and *usage of positive strategies* (see univariate statistics in Table 3).

Table 3: Sex-related differences in the SVF-78 - descriptive and statistic results

SVF-78 - Subscales	Sex	Mean	Standard deviation	*F value*	*p value*	*Partial Eta-Square*[1]
Downplay	female	6.66	3.88	**9.10**	**.003***	**.024**
	male	7.94	4.32			
Blame rejection	female	9.65	4.14	**10.76**	**.001***	**.028**
	male	11.06	4.26			
Distraction	female	11.08	3.59	0.12	.731	0
	male	10.95	3.90			
Substitute gratification	female	9.48	4.82	**11.25**	**.001***	**.029**
	male	7.88	4.46			
Situation control	female	14.63	4.01	1.42	.233	.004
	male	14.13	4.16			
Reaction control	female	14.82	4.02	3.64	.057	.01
	male	14.03	4.06			
Positive self-instruction	female	12.96	4.84	0.11	.742	0
	male	12.79	5.09			
Need of social support	female	13.81	5.43	**31.38**	**.000****	**.077**
	male	10.86	4.82			
Avoidance	female	14.56	4.84	0.73	.392	.002
	male	14.14	4.58			
Flight	female	12.45	5.23	2.62	.106	.007
	male	11.53	5.88			
Rumination	female	18.41	4.54	**11.83**	**.001***	**.03**
	male	16.64	5.44			
Resignation	female	12.91	4.77	4.22	.041	.011
	male	11.84	5.32			
Self-incrimination	female	14.04	5.08	**7.31**	**.007***	**.019**
	male	12.63	5.11			
Usage of defense / devaluation strategies	female	8.16	3.47	**13.03**	**.000****	**.033**
	male	9.50	3.77			
Usage of distraction strategies	female	10.28	3.59	**5.51**	**.019***	**.014**
	male	9.41	3.60			
Usage of control strategies	female	14.13	3.47	2.19	.140	.006
	male	13.58	3.86			
Usage of positive strategies	female	11.32	2.68	0.06	.811	0
	male	11.25	3.00			
Usage of negative strategies	female	14.45	3.97	**8.64**	**.003***	**0.022**
	male	13.16	4.61			

*=significant on the α-level $p<.005$; **= significant on the α-level $p<.001$, SVF= Stress Coping Questionnaire (German: Stressverarbeitungsfragebogen), [1]Variance that can be explained by this variable after accounting for the variance explained by other variables in model

Big Five personality traits

In order to investigate the differences in the Big Five personality traits the subscales of the BFI-10 were compared between females and males. The MANOVA showed that the subscales of the BFI-10 *Neuroticism, Extraversion, Openness,* and *Agreeableness* showed significantly higher scores for females than males. There was no significant difference in the subscale *Conscientiousness* between females and males (Table 4).

Table 4: Sex-related differences in the BFI-10 – descriptive and statistic results

BFI-10 scales	Sex	Mean	Standard deviation	*F value*	*p value*	*Partial Eta-Square*[1]
Neuroticism	female	3.88	.82	**6.85**	**.009***	**.018**
	male	3.65	.92			
Extraversion	female	2.80	.98	**5.35**	**.021***	**.014**
	male	2.57	1.00			
Openness	female	3.48	1.04	**14.84**	**.000****	**.037**
	male	3.07	1.06			
Agreeableness	female	3.53	.79	**12.61**	**.000****	**.032**
	male	3.24	.82			
Conscientiousness	female	3.84	.88	1.27	.260	.003
	male	3.79	.87			

*=significant on the α-level $p<.005$; **= significant on the α-level $p<.001$, BFI-10=Big Five Personality Traits Inventory
[1]Variance that can be explained by this variable after accounting for the variance explained by other variables in model

4.2.2 Excurse: Exploratory results

The BFI results were compared via one sample test comparison with data of a sample randomly selected of the norm population (151). Detailed data of the norm population as well as the results of the one sample *t*-test comparison are described in Table 5. Comparing female study subjects with female norm population, the personality traits *Neuroticism, Extraversion,* and *Conscientiousness* differed significantly. Male study subjects had significantly higher *Neuroticism* scores as well as significantly lower scores of *Extraversion, Openness, Agreeableness,* and *Conscientiousness* when compared to the male norm population.

Table 5: Results of one sample test comparison

BFI-10 scales	Females* (n=631) M	SD	*t-value, p-value*	Males* (n=503) M	SD	*t-value, p-value*
Neuroticism	2.58	.92	***t*(191)=22.067, *p*=.000****	2.22	.79	***t*(191)=21.490, *p*=.000****
Extraversion	3.51	.98	***t*(191)=-10.016, *p*=.000****	3.43	.90	***t*(191)=-11.982, p=000****
Openness	3.49	.96	*t*(191)=-.109, p=.913	3.31	.89	*t*(191)=-3.157, p=002**
Agreeableness	3.49	.81	***t*(191)=.674, *p*=.501**	3.39	.78	***t*(191)=-2.601, p=010***
Conscientiousness	4.24	.76	***t*(191)=-6.34, *p*=.000****	4.05	.82	***t*(191)=-5.064, *p*=000****

*=Data of norm population from (151) were compared with data from study subjects (table 4), separately for women and men.

**= significant on the α-level $p<.001$; BFI-10=Big Five Inventory 10 (151)

In Figure 7 the mean values of the BFI-10 subscales are graphically compared with the mean values of the general population.

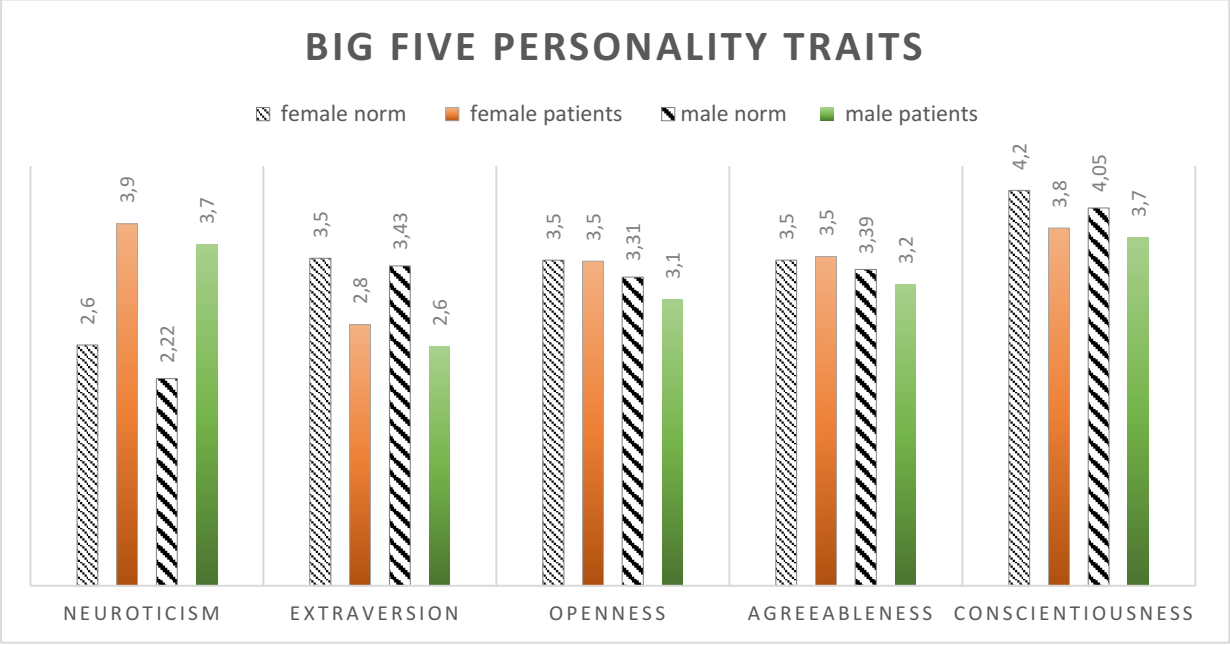

Figure 7: Big Five personality traits: Comparison between female and male patients and the general population

4.2.3 Physiological comorbidity and inflammatory bio-marker

Somatic comorbidity

Lipid disorders were the most frequent disorders in both female (52.06%) and male (61.31%) patients, followed by cardiovascular diseases (females 36.60%; males 51.55%). In Table 6 results are presented in detail. Sex-related differences were calculated with the χ^2 – test. Significant differences were found using the false discovery rate in hypertonia (females 25.77%, males 40.72%; χ^2 = 10.56a; p = .001) and in cardiovascular diseases (females 36.60%, males 51.55%; χ^2 = 9.33; p = .002) – higher in males – and thyroid dysfunction (females 34.54%, males 7.73%; χ^2 = 40.44; p = .000) and food intolerances (females 23.20%, males 7.22%; χ^2 = 18.41; p = .000) – higher in females.

Table 6: Sex-related differences in physiological comorbidities as diagnosed by the doctor

Physiological conditions	female % (n)	male % (n)	χ^2 *-value*	*p - value*
Hypertonia	25.77 (50)	40.72 (79)	**10.56**	**.001***
Lipid-related disease	52.06 (101)	61.31 (117)	3.12	.078
Thyroid dysfunction	34.54 (67)	7.73 (15)	**40.44**	**.000***
Diabetes mellitus	7.73 (15)	11.82 (21)	1.18	.278
Cardiovascular disease	36.60 (71)	51.55 (100)	**9.33**	**.002***
Obesity[1]	27.84 (54)	19.59 (38)	3.66	.056
Food intolerances (self-report)	23.20 (45)	7.22 (14)	**18.41**	**.000***

*=significant using a false discovery rate of .05
χ2 value= value of Chi-Square Test
n=number of patients
[1]=Obesity is defined as a Body mass index of 30 or more

BMI and obesity

The distribution of the BMI of the study subjects and the general population of Austria are displayed in Table 7. About 58% of females in this study were overweight or even obese, compared to only 39% of females of the general population. Of the male study patients, 68% were overweight or obese. In the general population 55% of the men were overweight or obese.

Obesity concerned 49% of overweight women in this sample, but only 29% of the male participants.

Table 7: BMI distribution of study patients and comparison with general population.

Body mass index distribution	Study Population		General Population*	
	female %	male %	female %	male %
BMI of 0-18.4	0.50	0.00	4.40	1.30
BMI of 18.5-24.9	41.70	32.30	56.70	43.60
BMI of 25-29.9	29.70	47.90	25.80	39.50
BMI of >30	28.10	19.80	13.10	15.70

*=Data from Statistik Austria (152); BMI=Body mass index

Blood pressure and heart rate

The cardiac variables did not have a normal distribution; therefore, differences were calculated with the Mann-Whitney-U-Test. Significant differences between females and males were found in systolic and diastolic blood pressure as well as heart rate at rest and peak. See Table 8 for descriptive and statistical results.

Table 8: Sex-related differences in health condition: cardiac variables - ergometer

Variables of health condition/fitness	Sex	Mean	Standard deviation	*Mann-Whitney-U Z score*	*p value*
Blood pressure systolic	female	136.61	17.66	**11843.5**	**.000***
	male	146.29	19.13		
Blood pressure diastolic	female	85.63	10.96	**14267.5**	**.000***
	male	89.55	12.10		
Heart rate (at rest)	female	95.09	13.04	**5632**	**.009***
	male	91.14	16.40		
Heart rate (peak value)	female	152.20	19.85	**6497.5**	**.012***
	male	149.82	20.60		

*=significant using a false discovery rate of .05

Inflammatory bio-marker

The bio-markers Trp, Kyn, and the Kyn/Trp ratio had a normal distribution; therefore, the t-test was performed. Significant sex-related differences occurred in Trp (females: M=62.28, SD=8.06; males: M=68.18, SD=7.97, $t(350)=-6.91$, $p=.000$) and the Kyn/Trp ratio (females: M=.030, SD=.008; males: M=.028, SD=.006, $t(350)=2.8$, $p=.006$). For an overview see Table 9.

Table 9: Sex-related differences in bio-marker - descriptive and statistic results

Blood parameter	Sex	Mean	Standard deviation	*t value*	*p value**
Tryptophan	female	62.28	8.06	**-6.91**	**.000***
	male	68.18	7.97		
Kynurenine	female	1.86	0.49	-0.97	.331
	male	1.91	0.43		
Kynurenine/tryptophan ratio	female	0.030	0.008	**2.80**	**.006***
	male	0.028	0.006		

*=significant using a false discovery rate of .05

4.2.4 Treatment – Number and kind of medication

Drug prescription

The variable number of different medications did not have a normal distribution; hence, a Mann-Whitney-U Test was performed with sex as the group variable. There was no significant difference between females (M=1.24; SD=1.10) and males (M=1.58; S =1.04; $U=18.589$, $p=.829$). See also Table 10.

Sex-related differences concerning the prescription of different psychotropic substances were calculated with the χ^2 – Test to calculate distribution differences.

A significant difference between females and males was found in Bupropion (females: 3.61%, males: 12.89%; $\chi^2(1)=11.04$, $p = .001$) and Mirtazapine (females: 5.15%, males: 13.40%; $\chi^2(1) = 7.84$, $p = .005$) using the false discovery rate with a Cronbach alpha of 0.05. Both drugs were found to be prescribed to men significantly more frequently than to women. For descriptive and statistical results see Table 11.

Table 10: Sex-related differences in number of different medications

Number of drugs	Female % (n)	Male % (n)
0	15.50 (30)	15.50 (30)
1	32.00 (62)	32.00 (62)
2	33.50 (65)	35.60 (69)
3	14.40 (28)	13.40 (26)
4	3.10 (6)	3.10 (6)
5	1.5 (3)	0.50 (1)

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%=percent of females / males; n=number of patients

Table 11: Sex-related differences in prescription of medication, descriptive and statistical results

Medication substance	Female % (n=194)	Male % (n=194)	*χ2 -value*	*p value**
SSRI	48.454	37.629	4.64	.031
Atypical neuroleptics	11.86	12.37	1.02	.600
Typical neuroleptics	7.73	5.15	1.07	.301
Lithium	0	0.52	1.00	.317
Duale antidepressants	23.71	24.74	0.06	.813
Bupropion	3.61	12.89	**11.04**	**.001***
Trazodone	41.75	35.05	1.84	.175
Mirtazapine	5.15	13.40	**7.84**	**.005***
Tricyclics	4.64	2.06	1.99	.158
Hypnotics	7.73	8.25	0.035	.851
Antiepileptics	6.70	6.19	0.043	.836

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*=significant using a false discovery rate of .05

χ2 Value=Value of chi-square test

n=number of patients

SSRI= Selective serotonin reuptake inhibitor

4.3 Objective II – Sex differences in changes during a six-week psychiatric rehabilitation program

Changes in clinical psychological scales (BDI-II, HAMD)

The MANOVA showed a significant difference over time in the BDI score as well as a change in HAMD for men and women. The interaction was not significant for the BDI, but there was a significant interaction for the HAMD. A post-hoc test revealed that the HAMD score significantly decreased in both females and males after the rehabilitation program (women: $t(174)=12.55$, $p=.000$; men: $t(182) = 14.14$, $p=.000$.), but the change was more prominent for men (Females 38.75%, males 42.35%). For descriptive and statistic results see Table 12.

Table 12: Changes in BDI-10 and HAMD descriptive and statistical results

Scale (Inventory)	Sex	T1 mean (SD)	T2 mean (SD)	Time	Interaction
Beck Depression Inventory (BDI-10)	female	20.27 (9.96)	9.10 (9.50)	***F*=423.08 *p*=.000****	*F*=2.70 *p*=.102
	male	20.58 (11.13)	11.06 (10.09)		
Hamilton Depression Scale (HAMD)	female	11.04 (6.26)	6.63 (5.51)	***F*=307.42 *p*=.000****	***F*=0.81 *p*=.041***
	male	12.82 (7.42)	7.24 (5.94)		

*=significant on the α-level p<.005; **=significant on the α-level p<.001

SD=standard deviation; T1=time of admission; T2=time of discharge;

4.3.1 Changes in coping styles

The multivariate analysis of variance with repeated measures was performed. For descriptive and statistical results see Table 13. The subscales of the SVF-78 *downplay*, *blame rejection*, *self-incrimination,* and the global scale *negative strategies* changed significantly between T1 and T2, but there was no significant interaction of time and sex. The subscales *avoidance*, *flight*, *rumination,* and *resignation* showed a reduction of the scale scores – but only the subscale *rumination* showed a significant interaction of time and sex. A post-hoc test revealed that the scores decreased in all patients significantly, but in women the difference between T1 and T2 was higher. Women showed a reduction of 17.77%, men a reduction of 12.63%. The subscales *situation control*, *distraction,* and *substitute gratification* showed a significant difference in

time – there was a significant increase of the scale scores – but only the subscale *distraction* showed a significant interaction of time and sex. A post-hoc test revealed that the scores increased in all patients significantly, but in women, the difference between T1 and T2 was higher. Women showed an increase of 14.74%, men only an increase of 4.99%. No significant results were found concerning the subscale *reaction control*. The subscales *positive self-instruction* and *need of social support resignation* showed a significant difference between T1 and T2 but no significant interaction of time and sex. There was a significant increase of *positive self-instruction* and *need of social support resignation* over time. The three global scales of positive coping strategies (*usage of defense / devaluation strategies, usage of distraction strategies,* and *usage of control strategies*) showed a significant difference in time – there was a significant increase of the scale scores – but only the scale *usage of distraction strategies* showed a significant interaction of time and sex. A post-hoc test revealed that the scores significantly increased in all patients, but in women the difference between T1 and T2 was higher. Women showed an increase of 11.66%, men only an increase of 5.25%.

Table 13: Changes in coping strategies (SVF-78) - descriptive and statistical results

Scale of SVF - 78	Sex	T1 mean (SD)	T2 mean (SD)	Repeated measure	Interaction
Downplay	female	6.71 (3.86)	8.70 (4.26)	**F= 59.20**	*F*= 2.56
	male	7.95 (4.26)	9.26 (4.74)	***p*=.000****	*p*=.111
Blame rejection	female	9.72 (4.15)	11.33 (3,98)	***F*= 35.21**	*F*= 0.72
	male	11.15 (4.30)	12.36 (4.31)	***p*=.000****	*p*=.397
Self-incrimination	female	14.01 (5.15)	11.57 (5,02)	***F*=95.35**	*F*=0.18
	male	12.77 (5.19)	10.53 (5.23)	***p*=.000****	*p*=.676
Avoidance	female	14.52 (4.83)	14.43 (4.59)	***F*=4.44**	*F*=3.00
	male	14.34 (4.57)	13.43 (4.22)	***p*=.036***	p=.084
Flight	female	12.37 (5.24)	10.94 (5.24)	***F*= 27.89**	F=0.02
	male	11.74 (5.83)	10.40 (5.60)	***p*=.000****	*p*=.879
Rumination	female	18.45 (4.67)	15.17 (5.52)	***F*=103.69**	***F*=5.10**
	male	16.54 (5.42)	14.45 (5.34)	***p*=.000****	***p*=.025***
Resignation	female	12.97 (4.83)	10.25 (5.14)	***F*=99.03**	*F*=2.16
	male	12.01 (5.28)	9.99 (5.12)	***p*=.000****	*p*=.143
Situation control	female	14.83 (3.91)	15.51 (3.56)	***F*=12.64**	*F*= 0.02
	male	14.18 (4.07)	14.80 (3.91)	***p*=.000****	*p*=.889
Reaction control	female	15.02 (4.00)	14.68 (3.48)	*F*= 0.08	*F*= 1.94
	male	14.08 (3.89)	14.30 (3.48)	*p*=.775	*p*=.165
Distraction	female	11.21 (3.45)	12.86 (3.72)	***F*=32.42**	***F*=8.02**
	male	11.12 (3.88)	11.68 (3.44)	***p*=.000****	***p*=.005***
Substitute gratification	female	9.43 (4.71)	10.17 (4.30)	***F*=9.04**	*F*=0.55
	male	7.88 (4.55)	8.33 (4.32)	***p*=.003***	*p*=.459
Positive self-instruction	female	13.23 (4.84)	14.77 (4.55)	***F*=35.84**	*F*=0.28
	male	12.86 (5.06)	14.15 (4.99)	***p*=.000****	*p*=.597
Need of social support	female	13.80 (5.43)	14.70 (5.10)	***F*=15.62**	*F*=0.00
	male	10.86 (4.80)	11.77 (4.73)	***p*=.000****	*p*=.979

*=significant on the α-level p<.005; **= significant on the α-level p<.001

SD=standard deviation; T1=time of admission; T2=time of discharge

SVF-78= Stress Management Questionnaire (German: Stress-Verarbeitungs-Fragebogen 78)

Table 13 continued: Changes in coping strategies (SVF-78) - descriptive and statistical results

Scale of SVF - 78	Sex	T1 mean (SD)	T2 mean (SD)	Repeated measure	Interaction
Usage of defense / devaluation strategies	female	8.21 (3.48)	10.01 (3.67)	***F*=62.83**	*F*=1.97
	male	9.55 (3.80)	10.81 (4.04)	***p*=.000****	*p*=.161
Usage of distraction strategies	female	10.34 (3.47)	11.55 (3.48)	***F*=29.51**	***F*=5.08**
	male	9.50 (3.61)	10.00 (3.39)	***p*=.000****	***p*=.025***
Usage of control strategies	female	14.33 (3.37)	14.98 (3.06)	***F*=18.06**	*F*=0.19
	male	13.62 (3.79)	14.42 (3.59)	***p*=.000****	*p*=.667
Usage of negative strategies	female	14.48 (4.00)	12.02 (4.49)	***F*=109.91**	*F*=1.63
	male	13.27 (4.62)	11.34 (4.68)	***p*=.000****	*p*=.202

*=significant on the α-level p<.005; **= significant on the α-level p<.001

SD=standard deviation; T1=time of admission; T2=time of discharge

SVF-78= Stress Management Questionnaire (German: Stress-Verarbeitungs-Fragebogen 78)

4.3.2 Changes in Kyn, Trp, and Kyn/Trp ratio

A multivariate analysis of variance (MANOVA) with repeated measures was performed to investigate changes during rehabilitation with a focus on Kyn, Trp, and Kyn/Trp ratio. There was no significant difference between T1 and T2 as well as no significant interaction between time and sex for Trp. The Kyn as well as the Kyn/Trp ratio showed a significant interaction between time and sex, but no significant difference in time. For details see Table 14. A post-hoc test revealed that the scores changed significantly only in male patients. Kyn significantly increased in males but not in females (women: $t(164)=1.72$, $p=.088$; men: $t(172)=2.22$, $p=.028$). Furthermore, the Kyn/Trp ratio significantly increased in males and not in females (women: $t(164)=1.90$, $p=.059$; men: $t(172)=2.47$, $p=.014$).

Table 14: Changes in inflammatory parameter

Blood parameters	Sex	T1 mean (SD)	T2 mean (SD)	Repeated measure	Interaction
Tryptophan	female	62.34 (8.07)	62.18 (8.22)	*F*=0.02	***F*=0.20**
	male	68.16 (7.95)	68.45 (8.37)	*p*=.889	***p*=.006***
Kynurenine	female	1.88 (.49)	1.83 (.47)	*F*=0.08	***F*=7.71**
	male	1.91 (.42)	1.97 (.42)	*p*=.774	***p*=.006***
Kynurenine/ Tryptophan ratio	female	.030 (.008)	.030 (.007)	*F*=0.00	***F*=9.62**
	male	.028 (.006)	.029 (.006)	*p*=.958	***p*=.003***

*=significant on the α-level $p<.005$; **=significant on the α-level $p<.001$

SD=standard deviation, T1=time of admission; T2=time of discharge

4.4 Objective III – Determinants of severity of depressive symptoms

A stepwise regression analysis was performed to estimate the weights of the regression coefficients predicting the severity of depressive symptoms (measured with BDI sum score at T1). The predictors were the BFI-10 subscales *Neuroticism, Extraversion, Openness, Agreeableness,* and *Conscientiousness*, and the SVF-78 global scales *usage of defense / devaluation strategies, usage of distraction strategies, usage of control strategies,* and *usage of negative strategies*. The model that best fit the data was one where *Neuroticism, Extraversion*, *negative coping strategies, defense / devaluation strategies,* and *distraction strategies* were included in the regression analysis. *Openness, Conscientiousness*, and *Agreeableness,* as well as *usage of control strategies* were deleted from the model because they were not able to explain any additional variance. The adjusted R square (portion of explained variance by the regression coefficients) was .402 with a standard error of 8.16.

In a second step, a regression analysis was performed separately for women and men with the five predictors resulting from the stepwise regression analysis. The adjusted R Square was .310 for females and .48 for males, meaning 31% or 47.1% of the variance is explained by this model. The regression analysis showed that for women the personality trait *Neuroticism* (B=0.916, t=2.02, p=.045) and *negative coping strategies* (B=1.15, t=5.70, p=.000) were significant determinants in predicting the severity of depressive symptoms. For men the personality trait *Extraversion* (B=-.775,t=-2.46, p=.015) as well as the *usage of distraction*

strategies (*B*=-.490, *t*=-2.74, *p*=.007) and *usage of negative coping strategies* (B=1.536, t=9.17, *p*=.000) were the strongest determinants predicting the severity of depressive symptoms (for statistical results see Table 15and Table 16).

Table 15: Prediction of BDI at T1: statistical results of regression analysis

Model Summary	**Female**	**Male**
R	.573	.704
R Square	.329	.496
Adjusted R Square	.310	.471
Std. Error of the Estimate	8.50	7.93
Significance of Model	***F*=17.81, *p*=.000****	***F*=35.71, *p*=.000****

R=correlation coefficient

The model equations to predict the severity of depressive symptoms in women and men which resulted from the multiple regression analysis are displayed in Figure 8.

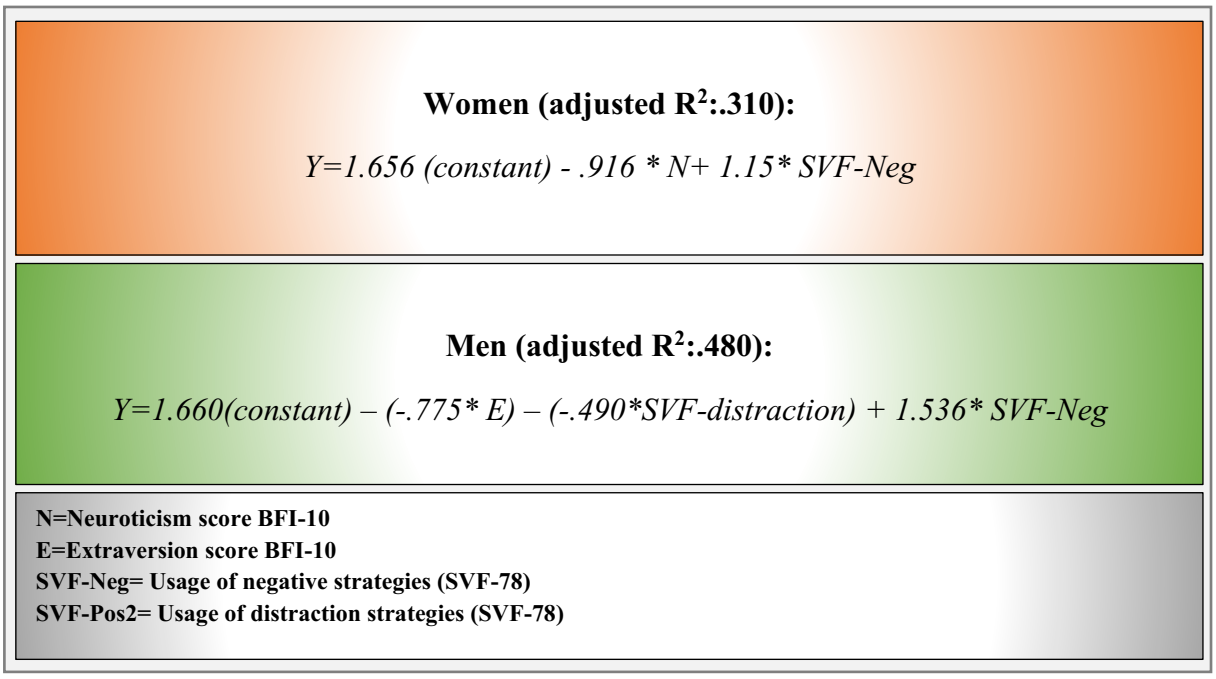

Figure 8: Model equation predicting severity of depression

Table 16: Prediction of BDI-II at T1: Further statistical results of regression analysis

Sex	Variables entered	Unstandardized coefficient B	Std. Error	Standardized coefficient Beta	*t value*	*p value*
Female	(Constant)	1.656	4.895	-	0.338	.736
	BFI-10 Neuroticism t1	0.916	0.453	0.148	**2.02**	**.045***
	BFI-10 Extraversion t1	-0.564	0.336	-0.109	-1.679	.095
	Usage of defense / devaluation strategies (SVF-78)	0.208	0.218	0.071	0.953	.342
	Usage of distraction strategies (SVF-78)	-0.361	0.194	-0.127	-1.865	.064
	Usage of negative strategies (SVF-78)	1.151	0.202	0.447	**5.696**	**.000****
Male	(Constant)	1.66	4.475	-	0.371	.711
	BFI-10 Neuroticism t1	0.425	0.348	0.072	1.222	.223
	BFI-10 Extraversion t1	-0.775	0.315	-0.142	**-2.464**	**.015***
	Usage of defense / devaluation strategies (SVF-78)	0.383	0.199	0.132	1.927	.056
	Usage of distraction strategies (SVF-78)	-0.49	0.179	-0.162	**-2.738**	**.007***
	Usage of negative strategies (SVF-78)	1.536	0.168	0.648	**9.169**	**.000****

*=significant on the α-level p<.005; **= significant on the α-level p<.001

SD=standard deviation; T1=time of admission; T2=time of discharge

SVF-78= Stress Management Questionnaire (German: Stress-Verarbeitungs-Fragebogen 78)

BFI-10=Big Five Personality Traits Inventory

5 Discussion

This study achieved three main aims:

- to find a difference in key depression variables (coping styles, personality traits, inflammatory bio-markers, and psychopharmacological treatment) between women and men with DD
- to investigate sex-related differences in treatment outcomes of a rehabilitation program. and
- to find determinants of severity of depression separately for women and men.

5.1 Sex differences in clinical key variables

Psychological variables - coping styles

The way a person reacts to stressful events can influence their psychological wellbeing (154, 155). The experience of stress and inadequate coping with stressful events has been found to be corelated with depressive symptoms and DD (156, 157). Females in this study more often choose stress coping strategies that are harmful to their self-esteem, namely *rumination* and *self-incrimination*, when dealing with stressful events, compared to their male counterparts. In recent studies, rumination, which is the tendency to think something over repetitively and thoroughly, was found to be highly correlated with sleep disturbances and depression (81, 25). Additionally, women showed significantly higher scores in the SVF subscales *substitute gratification* and *need of social support. Substitute gratification* as described by Janke is a stress coping strategy in which a person actively turns to a positive activity or situation in order to cope with a stressful or negative event (67). *Need of social support* is defined as the tendency to search for consultation from or social support of others when confronted with a stressful situation (67). Both coping styles can be harmful or beneficial depending on the context (67). Male subjects more often selected strategies beneficial to their self-esteem. Firstly, they showed higher scores in the subscale *downplay,* which is a stress coping strategy defined by a tendency to perceive others to be more stressed than oneself by a similar stressful situation (67). Secondly, male subjects showed higher scores in the subscale *blame rejection*, which is described as a tendency to emphasize the lack of one's own responsibility concerning the stressful event. The scale *usage of defense / devaluation strategies* is a global SVF-78 scale

combining the subscales *blame rejection* and *downplay* and it goes in line with the previous results that men also scored higher on this global scale. These findings are especially interesting because both groups, women and men, had a similar severity of depressive symptoms, and still women were more likely to use negative coping strategies. Coping strategies are known to play a crucial role in the development and treatment of depression (157). Their importance is further underlined by the findings of this study. Furthermore, the usage of negative coping strategies was a strong predictor for the severity of depression for men and for women. The results emphasize that learning to successfully cope with stressful events could be more important for women because they showed a tendency to use harmful strategies after a stressful event, such as the tendency to ruminate about the event and blaming themselves for what happened. This could explain some of the gender gap in the prevalence of depression, with women having a 1.5 to 2 times higher chance of suffering from a depressive disorder. The findings underline the importance of identifying and improving stress coping skills in the treatment of depression in women as well as men. Women might especially benefit from developing and / or improving healthy coping mechanisms.

Psychological variables – Big Five personality traits

Personality traits are further psychological variables with a strong association to depressive symptoms and DD. Certain personality traits can facilitate DD, others can serve as prevention of the disorders (158, 159). The most prominent personality trait strongly associated with depression is *Neuroticism* (97, 77). In this study, women showed significantly higher scores in *Neuroticism, Extraversion, Openness,* and *Agreeableness*. In accordance, sex differences in personality traits have been found in healthy adults (93, 160). In additional exploratory calculations, study subjects were compared with the general population separately for women and men. Women with a DD had significantly higher scores in *Neuroticism*, and significantly lower scores in *Extraversion* and *Conscientiousness* compared with women of the general population. Men had significantly higher scores in *Neuroticism* and significantly lower scores in *Extraversion, Openness, Agreeableness*, and *Conscientiousness* compared to the male norm population. However, the results showed that the existing differences in personality traits between women and men in general were not due to depression. Women scored higher in almost all personality traits compared to men. When comparing the two groups with healthy individuals, it becomes clear that certain personality constellations are more prone to facilitate

depressive symptomatology. High scores in *Neuroticism* and low scores in *Extraversion* and *Conscientiousness* seem to be strongly associated with depressive symptoms. In females, a high *Neuroticism* score was the strongest predictor for the severity of depression, while in males, a low *Extraversion* score was the strongest predictor for the severity of depression. This finding is remarkable and has not – to the best of the authors knowledge – been published before. The association of Big Five personality traits and depression has been investigated thoroughly, although scarcely with a main focus on sex. A recent study found that perceived stress can mediate the well-established relationship between Neuroticism and depressive symptoms (161). As described in the introduction, women report suffering from life events more often and being more sensitive to life events (70, 60); therefore they might be more affected by their *Neuroticism* value. Hence, *Neuroticism* might play the role of a mediator of the relationship between stress coping and depressive symptoms. An extensive literature research was not able to explain why *Extraversion* presented itself to be such a strong predictor for the severity of depression for men but not for women. A study by Gershuny showed low *Extraversion* and high *Neuroticism* scores very highly associated with depressive symptoms, but again there was no focus on sex differences (162). Furthermore, the results were not replicated in a follow-up study by Jorm (36). Further investigations are needed to shed light on this very interesting topic.

Somatic variables

In conjunction with the psychological variables related to depression, somatic conditions are also known to be strongly corelated to depressive symptoms. There is a known association between psychiatric and somatic disorders (14). The lives of persons severely affected by mental illness are scandalously short. For example, life expectancy for men with schizophrenia-spectrum disorders is 15.9 years and for women 13.6 years shorter compared to the general population (163). Yet the major reason people severely affected by mental illness die too soon is due not to suicide but mainly to preventable comorbidities (164). In addition, mental and physical health frequently share similar risk factors. Hence, physical health outcomes are worse when someone also has a mental health disorder, and mental health outcomes are worse when someone also has a physical health problem (165). Young adults with severe mental illness are five times more likely to have three or more physical health conditions than unaffected individuals at the same age (166). Data on the prevalence of somatic diseases in patients with a DD, however, remain sparse, especially when searching for a focal point on sex differences.

One of the most notable results of this work was the significant differences between females and males concerning thyroid dysfunction. More than a third of the females in this study showed a thyroid dysfunction, compared to only 8% of males. Correlations between depressive symptoms and thyroid dysfunction have been found in the past (15, 102). A study by Seck and colleagues, already more than 20 years ago, found that in healthy individuals 11.2% of females and 8% of males suffered from thyroid dysfunction (167). It is important to point out that the thyroid dysfunction rate in males did not differ between healthy and depressed individuals. Meanwhile, in females the prevalence was three times higher in depressed compared to healthy women. Epidemiological data showed that many disorders with sex differences in their prevalence are exacerbated by stress (168). Valentino et al. found a greater HPA dysregulation in females with psychiatric disorders and associated with stress as well as changes in several cellular and molecular mechanisms (168). Following this assumption, this could further lead to an increased endocrine arousal and an amplified emotional response to stress in women. In line with that, we found a significantly higher heart rate at rest and at time of high activity in women compared to men. The sympathetic nervous system has been found to be associated with the secretion and metabolism of the thyroid hormone (169). Furthermore, the thyroid hormone has been found to have a profound and direct effect on metabolism and cardiovascular functions (170) as well as on one's mental state. The hypothalamic–pituitary–thyroid (HPT) axis is affected by stress, and although the exact role of the HPT axis on the sympathetic nervous system remains controversial, alterations in the thyroid gland might cause and / or facilitate an imbalance in the sympathetic and parasympathetic nervous system (171). Reporting of digestion problems and irritable bowel syndrome has been connected with an imbalance in the sympathetic and parasympathetic nervous system activation, displaying a predominance in a sympathetic nervous activation (172). In line with these findings a quarter of the female study subjects reported suffering from food intolerances or digestive problems, only 7% of men had similar conditions. Moreover, a damaged microbiome has been associated with dietary disorder and metabolism disorders, which might be falsely interpreted as food intolerances (173). The microbiome and the brain-gut axis have come into focus in the life sciences in the last ten years. There is evidence that a damaged microbiome can affect wellbeing and mood and is correlated to DD through different inflammatory and endocrinological pathways (174–176). A recent study demonstrated a correlation between inflammatory cytokines and both symptoms of irritable bowel syndrome and the experienced quality of life (177).

The experience of stress has been connected to higher susceptibility to gastrointestinal diseases and has been found to enhance their severity. Acute as well as chronic stress can modulate the gut environment, fostering a dysbiotic microbiota, which has been linked to anxiety and DD (178). The results of this study support the presence of a relationship between biological mechanisms and emotional processes; nevertheless, the underlining pathways and mechanisms are yet to be studied and understood.

DDs are linked to metabolic disturbances, which are associated with low-grade proinflammatory states (179). The rate of cardiovascular diseases appeared to be considerably higher in patients with depressive symptoms compared to the general healthy public (180, 152). In line with that, cardiovascular diseases and hypertension were found to be significantly more frequent in male study subjects compared to females. It becomes evident that depressed individuals also have a greater risk of suffering from CVD or hypertension and vice versa, and this seems to affect men in a significantly higher proportion. Since there was no sex difference in obesity and diabetes mellitus, there must be another explanation for the higher rates in men. Progesterone and estrogen could serve as protective factors for women, as they influence antioxidative and oxidative parameters via DNA repair and activate antioxidative defense (181). Differences in the intake and number of specific drugs as well as sex-specific patterns in seeking help for illness might additionally contribute. This finding suggests that patients with depressive symptoms should be examined for heart diseases, and reversely patients with heart diseases should be screened for DD, since these two health conditions have a tendency to occur together (182). This is especially relevant for men with depressive symptoms, since they seem to have an overall higher risk of suffering from cardiovascular diseases.

BMI was equal in women and men, which was surprising to a certain degree since CVD and hypertension occurred more frequently in men and these conditions are strongly correlated with a higher BMI. However, the BMI is often criticized since it is an indirect measure of obesity and has its limitations (183). Compared to the general population, the BMI of the study participants was high, especially among women; a third more women with a DD were overweight or obese than women from the general population data pool. Obesity has been linked to DD in earlier research (184). The high prevalence of obesity might contribute as one factor for high comorbidity of depression and somatic illness. Nevertheless, no causal relation can be drawn. The two factors obesity and depression facilitate and worsen each other (185–187). This is the case for women as well as for men, although – as implied by the results of the

present study – depressed men are more at risk of being overweight, while on the other hand depressed women are more at risk of being obese. A review from recent years found evidence that being obese had a negative impact on treatment with antidepressants, while adding treatment for obesity to the treatment program of depression was beneficial for the treatment effect (188).

Kyn, Trp, and Kyn/Trp ratio

Kyn and Trp are known to be involved in serotonin metabolism. Since Kyn is a by-product of the Trp breakdown, the Kyn/Trp ratio is especially relevant, since it is an indicator of the proportion of breakdown of Trp to Kyn and therefore an indirect indicator for IDO. Because of the assumed neurotoxic qualities and involvement in inflammatory processes of Kyn and its byproducts, a higher proportion of Kyn to Trp ratio in depressed patients was expected (106–111). Furthermore, alteration in the further Kyn pathway products might lead to a higher susceptibility to mood disorders (110, 112). This association is partly mediated by low grade inflammation (189).

In this work, there was a significant sex-related difference in Trp, but not in Kyn value. Men showed a significantly higher Trp value than women. This consequently resulted in a lower Kyn/Trp ratio, meaning that the depressed males in this study population showed a more beneficial proportion of Kyn to Trp. There is a moderate number of studies describing female and male sex hormones and their interaction with Kyn pathway activation. In one study men showed an approximately 15% higher Kyn as well as Trp concentration when compared to women (147). The Kyn/Trp ratio was found to be increased during pregnancy, implying that changes in hormone levels are related do Kyn pathway activation (190). Furthermore, progestogen and estrogen were found to induce Kyn pathway activity, and androgens to inhibit Kyn pathways (191–194). The different hormonal status of women compared to men could explain some of the differences found in the Kyn and Trp levels at time of admission. This remains a speculation, since the hormonal status of women in this study was not assessed. A study by Hestad et al. (195) found that women with a DD had lower Trp levels compared to men, which is in line with the findings of the present study. Furthermore, Elovainio and colleagues found that the Kyn/Trp ratio could only predict depressive symptoms in females (196). Looking at further Kyn breakdown, a recent study showed a decrease in Kynurenic acid (Kyn A), which is one of the neuroprotective byproducts of Kyn, only in women. Additionally,

they found an association between the reduced Kyn A as well as increased CRP with the use of oral contraception (197). As mentioned above, IDO and its index (the Kyn/Trp ratio) is a biological mediator of inflammation, which is associated with the psychopathology of DD (195). The results of the present study imply that women, although equally depressed, seem to be affected more by a low-grade inflammation, since they have a higher Kyn/Trp ratio. This is in line with current research, which has stated that women are at a higher risk of suffering from low grade inflammation, due to multiple factors such as ovarian hormone fluctuations (46), interpersonal stressors, childhood adversity, obesity, and lack of physical activity (198). Hence women appear to be more susceptible to inflammation-related depressed moods and other neuropsychiatric disorders (198, 46).

Treatment differences

To improve individualized therapy, the assessment and analysis of the status quo of depression treatment is essential. Sex-related differences in drug prescriptions were identified in the present study. Men with depression were taking Mirtazapine nearly three times and Bupropion nearly four times more often than women. Concerning polypharmacy, a similar quantity of different drugs – an average of 1.5 drugs – was prescribed to women and men.

As a noradrenergic and specific serotonergic antidepressant, Mirtazapine is mainly used in the treatment of DD as well as anxiety and is known for its equivalent efficacy compared to tricyclic antidepressants. Prominent side effects of Mirtazapine are increase in appetite and bodyweight (199). Literature on the association of Mirtazapine and sex are scarce. One study found young men having an approximately 50 percent higher plasma level compared to women (200). A second study discovered a faster Mirtazapine metabolism in women compared to men, explained through differences in the genotype of the enzyme cytochrome P450 (CYP) 2D6 (201). Furthermore, a recent study on rats showed a stronger antidepressant effect in male compared to female rats (202). These findings might point to the assumption that Mirtazapine might be metabolized differently in women and men, which implies a better treatment response in men. This could in part explain why male patients received a Mirtazapine prescription more often than female patients. Furthermore, two studies found oral contraceptives to influence enzymes responsible for eliminating Mirtazapine (203, 204). Ultimately, the likelihood of sexually adverse drug reactions is known to be rather low in Mirtazapine compared to

serotonergic antidepressants (205, 206). Men might be at a higher risk of suffering from sexual dysfunction, at least in discussing sexual problems with their doctor (207). These findings, as well as the higher increase of appetite and weight associated with the intake of Mirtazapine, could lead to the observed sex-related differences in Mirtazapine prescription.

The antidepressant Bupropion is a dopamine and norepinephrine uptake inhibitor and is a substrate of the enzyme CYP2B6 (208), induced by estrogen (209). Higashi et al. postulated, that this interaction could lead to unexpected treatment outcomes in female patients taking oral contraceptives (209). Although the efficacy of Bupropion was not found to differ between sexes (210), a study found higher elimination half-life and higher maximum plasma concentration in women compared to men (211). Furthermore, women might be more vulnerable to the dopaminergic reward-enhancing effects of Bupropion (212), which can increase the risk of medication abuse (213). Considering sexually adverse drug reactions, Bupropion was found to induce increased libido (214), as well as to lead to less sexually adverse drug reactions (215). These findings could in part explain the higher prescription rate of Bupropion in men.

The number of psychotropic medications did not differ between sexes, with both groups taking an average of 1.5 drugs. These findings propose that women and men with a similar severity of depression are prescribed a comparable number of psychotropic drugs. The extent of polypharmacy was lower than expected. Previous studies found higher rates of polypharmacy (216, 137, 134, 136). Reasons for the different numbers could stem from the severity of depressive symptoms of the study subjects, ranging from mild to moderate. Comparative studies have investigated larger population samples, with a broader spectrum of severity of depressive symptoms (217, 127, 218). Large observational studies on population samples have a higher risk of a biased outcome, if samples of depressed males and females are compared, without a standardized diagnosis and matching of severity of depression and age. Women with mental problems tend to seek help more frequently and earlier than men (24, 13), and more willingly give information about their mental state (219). Men, on the other hand, more often choose self-medication with illegal or legal substances instead of seeking professional help (220). There might be a higher number of undiagnosed men with depression compared to women. Future research should therefore be conducted with severity-matched samples, using a valid diagnostic instrument.

In summary, the content of this thesis might give some indication that women and men might not respond the same way to treatment regimens for depression. The prevention of inadequate treatment strategies is of great importance.

5.2 Sex differences in changes during a six-week psychiatric rehabilitation program

The second objective of the dissertation was to investigate changes during a six-week rehabilitation program and potential differences between female and male patients in outcome parameters. Overall, the six-week rehabilitation program had a positive effect on the study population. Improvements were identified – with a few exceptions – in all psychological scales, with a tendency towards a slightly more beneficial effect in women.

Psychological changes during the rehabilitation program

The severity of depression (measured with BDI -II and HAMD) significantly decreased in the whole cohort, meaning there was an overall positive effect of the rehabilitation program on the severity of depressive symptoms. The initial coping strategies improved in the whole cohort during the treatment. Harmful strategies including *self-incrimination, negative strategies, avoidance, flight, rumination,* and *resignation* were reported to be used less, and beneficial strategies, such as *downplay, blame rejection, situation control, distraction, substitute gratification, positive self-instruction,* and *need of social support* were indicated to be used more often. Only the coping strategy *reaction control* did not change during the rehabilitation process. Sex-related differences were identified in the strategies *distraction* and *rumination*. Women and men showed a significant reduction of the usage of *rumination*; however, the decrease was stronger in women. Furthermore, women and men showed a significant rise in the usage of *distraction*; again the increase was stronger in women. These results indicate that women as well as men benefit from this six-week rehabilitation program on the psychological level; however, women seem to benefit to a greater extant in specific areas. A recent study in adolescents found females to engage more in interventions of mindfulness and report less stress after these interventions (221); however, another study concerning a stress prevention training showed no sex differences in the effectiveness of the training but found that women reported more health and stress complaints for and after the training (222). In a professional setting,

women more willingly give information about their emotional state compared to men (219) and in general are more likely to advance beyond an initial assessment when starting therapy (223). This could explain why they seem to benefit more from psychiatric rehabilitation programs. Due to masculinity stereotypes, it can be difficult for men to ask for help in managing their emotional life and to accept psychotherapy. In psychotherapy the male patient is expected to express his feelings and introspect as well as cooperate with the health care professional, which are all behaviors stereotypically attributed to women (219). Topics like self-esteem, emotions, and relationships are especially gender-salient (219). This could influence the outcome of the rehabilitation program. Furthermore, the association between inadequate stress coping and depressive symptoms is more dominant in women, as demonstrated above; therefore, a six-week rehabilitation setting, which eliminates major stressors like family, social relationship problems, and work overload could be more beneficial for women compared to men.

Studies investigating the efficiency of psychiatric rehabilitation programs remain sparse. A very recent Austrian study found evidence for the psychological effectiveness and cost efficiency of a psychiatric rehabilitation facility (224). To the knowledge of the author, no study has focused on the different treatment response of female and male patients with a DD undergoing psychiatric rehabilitation treatment programs, with the exception of the work of our study group (see (16)). Further research should focus on the question of how specific treatment strategies could help men and women both benefit more from psychiatric rehabilitation programs.

Changes in inflammation bio-markers during the rehabilitation program

Men showed an increase of Kyn and the Kyn/Trp ratio during rehabilitation treatment. Many factors determine Kyn levels in the blood and can lead to its alteration. As an example, a change of eating habits and workout regimes can lead to changes in the whole bio-psychological network and associated tryptophan breakdown. Several studies investigated changes in the Kyn pathways of Trp metabolism after physical exercise programs, and found beneficial changes in peripheral Kyn concentration in muscles, resulting in a decrease of Kyn and neurotoxic metabolites in cerebral regions (225, 226). However, other studies found conflicting results (189). Too little is known about the mechanisms of the Trp and Kyn breakdown, its byproducts, and how they affect the human brain, although the key role of the kynurenine pathway in energy metabolism and immune function has been established, as well as its possible manifestation in depression and other neuropsychiatric diseases as well as associated medical comorbidities

(189). Clarifying how stress, metabolism, inflammation and the endocrine system are connected and influenced by Kyn pathways of Trp metabolism will serve as an advancement of the field. Ongoing research in the field aims to establish Kyn and its byproducts as a biomarker to identify and prognose the course of psychiatric disorders, and herein lies huge future therapeutic potential. Furthermore, current research focuses on discovering novel pharmacological agents and treatment methods which potentially can manipulate Kyn and its byproducts in a beneficial way and therefore create additional therapeutic value in the treatment of DD as well as other neuropsychiatric diseases (189).

5.3 Conclusion

The main goal of this thesis was to investigate sex differences concerning psychological and physiological variables and treatment regimens to improve personalized care; therefore, relevant variables were compared between women and men and associated with the severity of depression. Additionally, changes during a psychiatric rehabilitation program in Austria were examined, and differences in the association of sex were investigated.

We found women and men with a similar severity of depressive symptoms to differ in certain psychological and physiological variables at time of admission to the psychiatric rehabilitation clinic. Importantly, these variables proved to be strongly associated with the severity of depressive symptoms.

Women and men showed differences in coping strategies. Men, although equally depressed, still showed more beneficial coping strategies, like *downplay*, *blame rejection,* and *defense / devaluation strategies*. Women, compared to men, more often tended to use harmful strategies, such as *rumination* and *self-incrimination*, but also showed higher scores in the strategies *substitute gratification* and *need for social support*, which can be beneficial strategies in the right context. *Negative coping strategies* were a strong predictor for women as well as men for the severity of depression. Developing a healthy coping response appears to be of major importance in the treatment and rehabilitation process of DD. After the six-week rehabilitation program, all patients showed a significant improvement in almost all coping strategies, namely an increase in the usage of beneficial and a decrease in harmful coping strategies. Interestingly, the female patients were able to compensate differences in the strategies that diverged at the beginning, having scores equal to men's in *blame rejection*, *downplay*, *self-incrimination,* and

rumination after the program. Men, on the other hand, could improve their scores of *need of social support* and *substitute gratification* but could not reach the level of their female counterparts. Overall, the improvement in the area of coping strategies was more dominant in women. This could lead to the assumption that the rehabilitation program was better suited for women than men. In line with that are the results of the inflammatory bio-markers Trp, Kyn, and the Kyn/Trp ratio. Men started out with a significantly higher Trp level and hence with a lower Kyn/Trp ratio, which is a marker of inflammatory processes assumed to be associated more directly to the level of serotonin in the brain (189) and is a better indicator of the neurotoxic qualities of the Trp and Kyn breakdown. Nevertheless, during the six-week rehabilitation program there was an increase in Kyn and thus also an increase in Kyn/Trp ratio in men. After a six-week rehabilitation program with the focus on healthy eating, sports, and psychological well-being, this result was very surprising. However, it could support the notion that the format of the psychiatric rehabilitation program is more beneficial to women than to men. Furthermore, women showed higher scores in four of the Big Five personality traits: *Neuroticism, Extraversion, Agreeableness,* and *Openness (to ideas)*. These differences can also be found in the healthy population. Interestingly, a higher value on *Neuroticism* was an important predictor for the severity of depression only in women, and a lower value in *Extraversion* a strong predictor for the severity of depression in men. This is a very important result. It could indicate that different psychological deficits facilitate the development of DD depending on the patient's sex. Therapeutic methods should focus on these differences.

Major differences were also found in the somatic variables. Over half of the men with depression suffered from CVD, about a quarter more than women. Health care professionals are advised to test for cardiovascular diseases in depressed patients, especially males, as well as test for affective disorders in patients with cardiovascular diseases, since the two illnesses show a tendency to occur together. This could improve life quality and expectancy in this risk group. Cardiovascular diseases are the main cause of death in industrial countries, so the focus should be on treating and preventing them and their concomitants. Thyroid dysfunction and digestive problems as well as elevated heart rate were more frequent in women. All these results appear to be connected to an imbalance or overregulation of the HPA-stress axis, harmful alterations of the microbiota, and low-grade inflammation. This leads to an overall inadequate response to stressful events, which seems to be more dominant in women with DD compared to men with DD.

Concerning medication, the investigated groups were similar. The number of drugs taken per person was equally high among women and men. Differences were found in the frequency of prescription of Bupropion and Mirtazapine, which was prescribed more often to men, which might be due to expected adverse side effects (weight gain, and adverse sexual side effects) and gender stereotype preconceptions.

Explanation for the gender gap in depression

The following explanation for the higher prevalence of depression in females could be extracted from this study. Women more often have higher rates of *Neuroticism* (in general and in study patients) and *Neuroticism* is highly associated with the development of anxiety and DD (77, 85). Furthermore, women tend to use inadequate and harmful coping strategies when dealing with stress, which could facilitate the development of the depression. Lastly, female study patients showed a three times higher rate in thyroid dysfunction. This might have an effect on the sympathetic nervous system and lead to increased anxiety and changes in mood states. Men, on the other hand, tend to dampen their emotions when coping with stressful experiences (87, 82, 84, 25) and due to cultural masculinity stereotypes often struggle to admit that they have a mental health problem and / or need professional help (219). Hence, the differences in prevalence could also be caused by the fact that they do not realize or do not acknowledge being affected by depressive symptoms. Thus, they might be equally depressed as women but unaware of or unable to express their feelings and, consequently, the gender gap in depression might be smaller than generally assumed.

Implication in theory and practice - What should be considered?

At present, there is a lack of evaluative studies investigating psychiatric rehabilitation response, especially in the context of DD. Furthermore, the influence of a patient's sex on the rehabilitation outcome has not been illuminated so far. The findings of this thesis can serve as additional components to improve the psychiatric rehabilitation process.

Due to the highly structured process of psychiatric rehabilitation treatment, the relatively long treatment period, as well as the maximal subacute current depressive symptomatology, the rehabilitation setting is ideal to work on stress management and coping strategies. Stress

management as well as coping with stressors is relevant in the therapeutic process of treating DD. Rumination and pessimistic thinking are especially harmful strategies that can be influenced by therapeutic methods including the aforementioned strategies. Women were shown to be more vulnerable to suffering from stressful events than men. Methods like relaxation techniques or breathing exercises as well as positive affirmations and cognitive restructuring have been proven to be effective in reducing stress, anxiety, and depressive symptoms (227). This could be very helpful in the psychiatric rehabilitation process, especially for women.

Furthermore, physical exercise can reduce stress and depressive symptoms, both on a clinical psychological as well as on a neurobiological level (228, 229). In addition, sports therapy could target relevant DD problems such as obesity and associated somatic comorbidities, which are crucial and negative prognostic factors in DD (187). Patients with mental illness are often in bad physical health condition, and this should be taken into account throughout the therapeutic process. A rehabilitation program has an emphasis on the development and preservation of stress resilience through physical exercise and healthy diet as well as psychotherapy and can therefore influence somatic comorbidities in addition to the improvement of depressive symptoms. Measuring outcome parameters – not only focused on clinical psychiatric symptoms but also including somatic parameters – are major strengths of the rehabilitation setting and should be investigated in clinical as well as research settings. As men seem to be especially vulnerable in the cardiovascular system and women concerning thyroid function in the context of depression, specific examinations might be useful.

Further, personality traits have been shown to be associated with depressive symptoms. As these traits are chronic factors, they are not to be influenced significantly during acute depressive treatment. Nevertheless, work on personality can be initiated in a rehabilitation setting. In the therapeutic process, *Neuroticism* as well as *Extraversion* values should be assessed. In women especially the program should focus on *Neuroticism* while in men training on *Extraversion* might be useful to further influence the severity of depressive symptoms.

Sex-specific pharmacological reflections are sparse to date. This should be improved with further research but also by asking women and men the same questions in the context of effects as well as side effects. At the moment, the risk of choosing a specific drug and neglecting another one because of sex-based prenotions and habit is possible. Individual needs and

conditions (relevance of sex drive, weight gain, and the intake of oral contraception) should be acquired and taken into account when making a decision concerning the treatment plan.

These important findings are relevant not only for the psychiatric rehabilitation setting but also for acute treatment in psychiatric hospitals and should find an application there as well.

Based on the data of the present study, I recommend that in addition to a bio-psycho-social health and illness model, gender-specific differences in treatment should be taken more into account to achieve optimized individualized therapy and treatment of each patient. Health care professionals should determine which main coping strategies the patient uses and which of them prove useful or harmful. In a further step, harmful strategies should be reflected on and, if possible, replaced with strategies beneficial to self-esteem and wellbeing.

Limitations and outlook for future work

This study showed a number of limitations that need to be outlined. First, 94% of the subjects were 40 years or older; therefore, conclusions and assumptions can mainly be made for this age group.

Second, due to the homogeneity of the sample, being mainly employees of the state (police force, army, teachers, public officials), wider representative of the general population of Austria is compromised; however, a higher validity of the data is achieved.

Third, implementing a longitudinal study, with a starting point before the onset of depression and with an additional measuring point six months after the rehabilitation program, would have suited the research question better but was not possible due to the lack of resources and because of the preexisting framework of the main study protocol. This particular study design would be a desirable goal in future research.

There are still a considerable number of unanswered questions concerning the biological and psychological differences in development and illness presentation of female and male patients suffering from DD, such as why the psychological and somatic conditions diverge to such a great extent between women and men and if these differences are causes or consequences of the depressive symptoms. Again, longitudinal studies with a starting point before the onset of the disorder could further help to clarify these issues.

Strengths and novelty

To the best of my knowledge, this thesis is the first to investigate sex difference in patients with DD with a well-matched sample in a case-control study design. The thesis provides scientific evidence to improve personalized care. We could highlight the importance of stress coping styles and personality traits in the development and treatment of female vs. male DD and identify major differences between the groups. These findings are of high value in daily clinical practice and future prospective longitudinal follow-up studies including a randomized-controlled design are needed. Additionally, dominant sex-related differences in cardiovascular diseases and thyroid dysfunction have been identified, which has not been described in this context before. Along the way, new insights concerning sex-related differences in the Kyn/Trp breakdown and its association with DD were gained. Furthermore, this thesis provides a unique portrait of psychopharmacological treatment regimes in Austria, focusing not only on medication frequency but also on sex differences in psychotropic prescriptions. In conclusion, this work provides important evidence for improving the treatment and therapy of patients with DD with a focus on gendered medicine and personalized care.

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7 Appendix

7.1 Sex-related differences in psychological comorbidity

Table 17: Sex-related differences in psychological comorbidity

Diagnose groups ICD-10	Female n=194 %(n)	Male n=194 %(n)	χ2 -value	*p - value*
F0 Organic, including symptomatic, mental disorders	0	0.52 (1)	-	-
F1 Mental and behavioral disorders due to psychoactive substance use	4.64 (9)	11.34 (22)	5.05	.023
F2 Schizophrenia, schizotypal and delusional disorders	0	0	-	-
F3 Mood [affective] disorders (F32/F33 excluded)	0	1.03 (2)	-	-
F4 Neurotic, stress-related and somatoform disorders	16.49 (32)	14.95 (29)	.175	.780
F5 Behavioral syndromes associated with physiological disturbances and physical factors	2.58 (5)	1.03 (2)	-	-
F6 Disorders of adult personality and behavior	2.58 (5)	4.64 (9)	1.17	.415
F7 Mental retardation	0	0	-	-
F8 Disorders of psychological development	0	0	-	-
F9 Behavioral and emotional disorders with onset usually occurring in childhood and adolescence	0	0.52 (1)	-	-
Z73 Problems related to life management difficulty – e.g., burnout syndrome	22.16 (43)	29.38 (57)	2.64	.131

χ^2 Value= Value of Chi-Square Test

n=number of patients