CHAPTER 1
GENERAL INTRODUCTION
Health impact, definitions and risk factors

Mental health problems cause immense suffering for millions of people around the globe. The most recent Global Burden of Disease data (1) demonstrates that they are currently the greatest single contributor to disability worldwide (2). Depression and anxiety are the most prevalent mental health disorders. One in six people will meet the criteria for a depressive episode or anxiety disorder in their lifetime (lifetime prevalence 15%) (3).

Depression and anxiety occur in all age groups but the onset is predominantly in early adulthood. Mental disorders, and depression in particular, are therefore the primary source of disability in young adults (4,5). The impact of these disorders on individuals and society is severe because they impair people at a crucial time in their lives when they are pursuing an education or career, forming relationships and starting families. The course of depression and anxiety disorders shows considerable variation in remission rates and chronicity, but overall relapse rates are high, as is comorbidity with other mental, substance use, and physical disorders (6). Researchers of the Global Burden of Disease of Mental Disorders Study Group conclude that: “In view of the magnitude of their contribution, improvement in population health is only possible if countries make the prevention and treatment of mental and substance use disorders a public health priority” (2).

This thesis includes studies on major depressive disorder (MDD) and the most common anxiety disorders: generalized anxiety disorder (GAD), social phobia (SP), panic disorder (PD) and agoraphobia (AP) as defined and described in the Diagnostic and Statistical Manual of Mental Disorders (DSM, fourth edition) by the American Psychiatric Association (7). In this classification system the core symptoms of major depressive disorder are the presence of depressed mood and/or loss of interest or pleasure (also known as anhedonia). Additional symptoms include appetite or weight change, sleep disturbance (insomnia or hypersomnia), psychomotor retardation or agitation, fatigue or loss of energy, feelings of worthlessness or excessive guilt, diminished ability to concentrate or indecisiveness and thoughts of death or suicide. MDD is defined as the presence of five or more of these symptoms, including at least one core symptom, for at least two consecutive weeks, causing marked distress or impairment.

The core symptom of generalized anxiety disorder is excessive anxiety or worry about multiple events or activities of daily life for at least six consecutive months. For a diagnosis of GAD this must be accompanied by three or more of the following symptoms: restlessness or feeling on edge, fatigue, difficulty concentrating, irritability, muscle tension, and sleep disturbance.

Social phobia (also known as social anxiety disorder) is characterized by a marked and persistent fear of one or more social situations in which one is exposed to possible scrutiny by others (or in which one could display anxiety symptoms), that will be humiliating or embarrassing. The situations invariably provoke this anxiety and therefore are avoided or endured with intense anxiety. People with social phobia recognize their fear as excessive or unreasonable, and it interferes markedly with social functioning.

A panic attack is a period of intense fear or discomfort, in which four (or more) of the following symptoms develop abruptly and peak within 10 minutes: palpitations, sweating, trembling, shortness of breath, feeling of choking, chest pain, abdominal distress, feeling faint, derealization or depersonalization, fear of losing control, fear of dying, numbness, chills or hot flushes. Panic disorder is characterized by recurrent unexpected panic attacks, which are followed by a period of at least one month with at least one or more of the following symptoms: persistent concern about having additional attacks, worry about the consequences of an attack, or a change in behavior related to the attacks. Panic disorder is often accompanied by agoraphobia, marked anxiety about being in places from which escape might be difficult (or embarrassing) or in which help might not be available in the event of having panic symptoms. Typically these situations include being outside of the home alone, in a crowd or queue, or travelling in public transportation.

Although the DSM defines distinct diagnoses for depression and anxiety disorders, they very often co-occur; with comorbidity rates around 60%, and lifetime comorbidity as high as 80% (8). In most people with MDD at least some anxiety symptoms are present if they do not meet the full criteria for an anxiety disorder, and vice versa.

Depression and anxiety disorders share the same risk factors which include female sex (women have a twofold increased risk compared to men), lower socioeconomic status or educational attainment, financial or social problems, (un)employment, being part of an ethnic minority, absence of an intimate partner relationship, a recent negative or stressful life-event (such as job loss, or death of a close friend or relative) (6). Childhood trauma (emotional neglect, physical or sexual abuse) is a particularly important factor that increases the risk of developing depression more than twofold, and is predictive of a more severe course (9).
Lifestyle, physiological & somatic risk factors of depression and anxiety disorders

Besides the risk factors mentioned above depression and anxiety disorders are associated with a number of lifestyle factors, physiological stress markers and (risk of) somatic diseases. Depression has been associated with cigarette smoking, alcohol use, (lack of) physical activity, poor diet and higher body mass index (BMI) (10–14). These are bidirectional associations; these lifestyle factors are accompanied by an increased risk of developing affective disorders, but people with these disorders are also more likely to engage in these lifestyle behaviors.

Unhealthy lifestyle factors are well-established risk factors for most major age-related chronic diseases, including cardiovascular disease, type 2 diabetes, and cancer as well as all-cause mortality. Depression and anxiety are associated with an increased risk of somatic diseases and mortality (15). This is also a bidirectional association, as somatic poor health is also a risk factor for developing depression and anxiety (16). Part of the association between affective disorders and somatic ill health can be explained by the abovementioned lifestyle factors, however even when taking those into account, affective disorders carry an increased risk for morbidity and mortality.

There is increasing evidence to suggest that the increased risk of morbidity may be caused by heightened activity of the body’s physiological stress systems, the inflammatory system, the hypothalamic-pituitary-adrenal axis and the autonomic nervous system. Increased levels of inflammatory makers have been demonstrated in depression (17), and there is some preliminary evidence suggesting anti-inflammatory medications are effective (add-on) treatments for depression (18). The hypothalamic-pituitary-adrenal axis (HPA-axis) that regulates the production and release of the stress-hormone cortisol show signs of chronic over-activity in depression, causing increased levels of cortisol and a decreased responsiveness of the system as a whole (19). The autonomic nervous system (ANS) may also be hyperactive; subjects with depression have higher resting heart rates than controls, and show signs of increased sympathetic and decreased parasympathetic nervous system activity (20), however current findings are inconsistent. Antidepressant use is an important factor in this association (21), affecting both sympathetic and parasympathetic activity, negatively impacting the overall autonomic activity profile (22). Finally both depression and anxiety disorders have been associated with accelerated cellular ageing (23,24), as measured by telomere length, the non-coding DNA structures at the end of chromosomes there to protect the DNA from damage.

Oxidative stress is a well-established mechanism in both ageing and major chronic diseases (25), and is predictive of mortality (26). It is related to heightened physiological stress states and is a key mechanism in physiological ageing (27). The role of oxidative stress in depression and anxiety disorders is therefore worthy of further exploration.

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**WOMEN AUTHORS ON DEPRESSION**

“Others imply that they know what it is like to be depressed because they have gone through a divorce, lost a job, or broken up with someone. But these experiences carry with them feelings. Depression, instead, is flat, hollow, and unendurably. It is also tiresome. People cannot abide being around you when you are depressed. They might think that they ought to, and they might even try, but you know and they know that you are tedious beyond belief: you are irritable and paranoid and humorless and lifeless and critical and demanding and no reassurance is ever enough. You’re frightened, and you’re frightening, and you’re “not at all like yourself but will be soon,” but you know you won’t.”

— Kay Redfield Jamison, *An Unquiet Mind: A Memoir of Moods and Madness*

“Depression is the most unpleasant thing I have ever experienced . . . . It is that absence of being able to envisage that you will ever be cheerful again. The absence of hope. That very deadened feeling, which is so very different from feeling sad. Sad hurts but it’s a healthy feeling. It is a necessary thing to feel. Depression is very different.”

— J.K. Rowling

“The reason why I hadn’t washed my clothes or my hair was because it seemed so silly. I saw the days of the year stretching ahead like a series of bright, white boxes, and separating one box from another was sleep, like a black shade. Only for me, the long perspective of shades that set off one box from the next had suddenly snapped up, and I could see day after day glaring ahead of me like a white, broad, infinitely desolate avenue. It seemed silly to wash one day when I would only have to wash again the next. It made me tired just to think of it.”

— Sylvia Plath, *The Bell Jar*
OXIDATIVE STRESS

What is oxidative stress?
Oxidative stress refers to an imbalance between oxidants and antioxidants, in favour of the oxidants, and the biological damage this causes (25). Oxidants are capable of oxidizing other substances by taking electrons from them. By accepting electrons, oxidants become negatively charged molecules with one or more unpaired electrons, also known as free radicals. Free radicals derived from oxygen are the most important class and are also known as reactive oxygen species (ROS). The unpaired electrons make these molecules highly reactive and unstable (28).

The most important endogenous source of ROS are the mitochondria. The primary function of these organelles is energy production by creating adenosine triphosphate (ATP) through the electron transport chain in which the major products of glucose are oxidized. This process is also known as aerobic respiration and is dependent on oxygen. This form of energy production is highly efficient and was therefore a key event in the evolution from single cell anaerobic organisms to complex multicellular aerobic organisms. The electron transport chain however “leaks” ROS, as a normal by-product of ATP production. ROS perform a number of beneficial physiological roles in cellular signalling and in the defence against pathogens, where their reactive properties are used to attack invading microorganisms. However, their reactivity also means they have potentially damaging effects to proteins, lipids and DNA.

To protect against these harmful effects, all aerobic organisms have developed a range of enzymatic and non-enzymatic antioxidant defences. These antioxidants defences include antioxidant enzymes (such as superoxide dismutase [SOD], glutathione peroxidase and catalase) and non-enzymatic antioxidants (including ascorbic acid [vitamin C], alpha-tocopherol [vitamin E], glutathione [GSH], carotenoids and flavonoids) (25). There are a range of mechanisms for antioxidant defence including: agents that remove ROS by catalysis (e.g. SOD), agents that decrease ROS formation, quenching of ROS (e.g. carotenoids), agents that are preferentially oxidized to preserve more important biomolecules (e.g. uric acid), and replacement of molecules sensitive to oxidative damage with those resistant to it (28).

Maintaining “redox homeostasis”, the balance between the useful properties of ROS and their potentially damaging effects, is an important feature of the biology of all aerobic organisms. If redox regulation falls short, either because ROS are present in excess (due to increased production or environmental exposure) or in case of compromised defences (a lowered antioxidant status) oxidative damage occurs to lipids, proteins and DNA which disrupts normal cell metabolism, causing cellular dysfunction and ultimately cell death (25).

Besides endogenous mitochondrial production of ROS there are many exogenous environmental sources or ROS or factors that increase oxidative stress. These include among others tobacco smoke, alcohol consumption, (ultraviolet)radiation, air pollution, heavy metals and pesticides (29). In addition, oxidative stress is closely related to the inflammatory response, with inflammation increasing oxidative stress and vice versa in an increasing cycle, together causing cellular damage and dysfunction (30).

Oxidative stress has been implicated in physiological ageing since what is now called the “oxidative stress theory of ageing” was first proposed by Harman over half a century ago (27). The core idea of this theory is unchanged: oxidative stress causes wear and tear at the macromolecular level, and this damage accumulates over a lifespan leading to decline of cellular function. Most major age-related diseases have been associated with increased oxidative stress and/or decreased antioxidant status, including cardiovascular disease (31), cancer (32), neurological (33) and psychiatric disorders (34).

Markers of oxidative stress
There is no single preferred or gold-standard marker of oxidative stress. Markers of oxidative stress are currently essentially not used in the routine practice of clinical medicine. But there are a number of possible approaches to estimate oxidative stress levels in the body (35).

ROS themselves are by definition highly reactive and consequently have short half-lives making measurement extremely difficult, but they can be captured through radical trapping techniques. There are also assays available for a wide range of antioxidant enzymes and non-enzymatic antioxidants, that include well-known antioxidants such as ascorbic acid (vitamin C) and tocopherol (vitamin E) (28). Measuring either ROS or antioxidants is informative, but each reflect only one side of the redox homeostasis, leaving the question unanswered what the outcome of the interaction between the two is. Specific markers reflecting oxidative damage to lipids, proteins or DNA (35) can provide more information as they represent the outcome of exposure to ROS and the activity of the antioxidant defenses.

This thesis will focus in particular, but not exclusively, on two plasma markers of oxidative damage: 8-OHdG and F2-isoprostanes, which reflect oxidative damage to DNA and lipids respectively. Both markers are described in more detail in the methods paragraph of this chapter.
**ARE DEPRESSION AND ANXIETY ASSOCIATED WITH OXIDATIVE STRESS?**

**Current evidence on depression, anxiety and oxidative stress**

Oxidative stress is worth exploring in depression and anxiety disorders from a number of perspectives. Firstly, oxidative stress may be part of the pathophysiological mechanism that explains the association between these disorders and the increased risk of somatic disease and mortality. Secondly, increased oxidative stress, either through (unhealthy) lifestyle or possible mitochondrial dysfunction may cause oxidative damage to the brain, making an individual more vulnerable to developing affective disorders. Thirdly, if oxidative stress is associated with affective disorders, markers of oxidative stress could be useful in clinical practice to predict course or treatment response. Finally, if oxidative stress is a contributing mechanism to affective disorders (in some subgroups of patients), decreasing oxidative stress or strengthening antioxidant defences could be new avenues for treatment.

At the start of this thesis there was some evidence to suggest oxidative stress is higher and antioxidant capacity is lower in depression and anxiety disorders (36). A few examples of the existing evidence include one study on 8-OHdG and one on F2-isoprostanes in approximately 80 MDD outpatients which demonstrated higher levels of both markers compared to controls (37,38). Superoxide dismutase (SOD) was found to be upregulated in multiple studies on both MDD and anxiety disorders (39–41), possibly as a response to increased exposure to oxidative stress. There were also reports of lower levels of well-known non-enzymatic antioxidants such as vitamin E (42) and vitamin C (39) in depression, but also multiple studies with conflicting findings, reporting no or even inverse associations (43–48). A meta-analysis (36) on both oxidants and antioxidants reported very high heterogeneity (±80-90%), reflecting highly inconsistent findings across studies.

Most studies had relatively small sample sizes (between 50 and 150 subjects) and many lack data on important lifestyle factors that could be potential confounders. Use of antidepressant medications, which have been demonstrated to affect oxidative stress and antioxidant measures, are also not accounted for in a considerable number of studies. In addition many studies used measures that may not be sufficiently specific to be considered valid markers of oxidative stress.

Overall, the size and scope of the evidence for an association between oxidative stress and depression is limited; and anxiety disorders are only explored in a handful of studies. Consequently, even though there are reasons to believe that oxidative stress is associated with depression and anxiety disorders, the current overall evidence is limited. This forms the main rationale for the conducting the further studies on this topic.

**Determinants of oxidative stress and associations with other stress systems**

Markers of oxidative stress are increasingly being studied in both somatic and psychiatric disorders to increase understanding of their pathophysiology, to identify biological makers that predict the prognosis or treatment outcome, and eventually to find novel therapies. This thesis therefore also covers topics to advance the field of oxidative stress research in general.

As described above there is no gold-standard single measure of oxidative stress. There is also no clear consensus on how sampling, sociodemographic, health and lifestyle variables should be accounted for in studies on oxidative stress in all fields of medicine. There is a lot of variation in whether, how and which factors studies include. This may contribute to a considerable proportion of the heterogeneity in oxidative stress research.

To adequately interpret current findings and inform future research on the many disorders, including psychiatric disorders, in which oxidative stress is involved, a clear understanding of which factors determine levels of oxidative stress markers in needed. Therefore a chapter of this thesis is devoted to studying a wide range of sampling, sociodemographic health and lifestyle determinants of oxidative stress. These findings in part inform the methodology for the studies conducted on the main aim, the association between oxidative stress and depression and anxiety disorders, supplying a strong rationale for the covariates included in these studies.

Secondly, based on current knowledge of chronic stress responses, oxidative stress is likely associated with other major physiological stress systems including the inflammatory system, the hypothalamic-pituitary-adrenal axis and the autonomic nervous system. All of these systems have also been implicated in depression and anxiety disorders. Whether and how the systems are associated, and whether this association is impacted by the presence of psychopathology, however not been yet been investigated.
Central aims of this thesis
The main objective of this thesis is to establish whether there is an association between oxidative stress and depression and anxiety disorders; hypothesizing oxidative damage will be higher and antioxidants lower in these disorders. The central aims can be summarized as follows:

1. To establish the key sampling, sociodemographic, lifestyle and health determinants of oxidative stress by investigating the cross-sectional associations between makers of oxidative damage and sociodemographics, (unhealthy) lifestyle factors and (risk factors for) chronic disease (Chapter 2).

2. To establish:
   a. The cross-sectional associations between oxidative damage or antioxidants and major depressive disorder, anxiety disorders and depressive symptoms (Chapters 3-6).
   b. The longitudinal associations between oxidative damage or antioxidants and major depressive disorder, anxiety disorders and depressive symptoms, and to ascertain whether depressive symptoms predict future oxidative damage and antioxidants levels, and/or vice versa (Chapters 4 & 6).

3. To establish the cross-sectional association between oxidative stress and three other major physiological stress systems: the inflammatory system, the hypothalamic pituitary adrenal axis and the autonomic nervous system. (Chapter 7).

METHODS

Cohort studies in this thesis
The Netherlands Study of Depression and Anxiety (NESDA) is an ongoing observational cohort study that aims to identify the social, psychological, biological and genetic factors that determine the onset and course of depressive and anxiety disorders. A total of 2,981 participants were included between 2004-2007 from three sites in the Netherlands (Amsterdam, Leiden and Groningen). This sample includes subjects between 18 and 65 years old with a current (57%) or remitted (21%) depressive or anxiety disorder and control subjects with no lifetime history of any psychiatric disorder (22%). Participants were recruited from the community, primary care and specialized mental health care, in order to obtain a sample representative of a broad range of depressed and anxious subjects. Exclusion criteria were insufficient command of the Dutch language, a primary clinical diagnosis of bipolar disorder, obsessive-compulsive disorder, posttraumatic stress disorder (PTSD), a substance use or a psychotic disorder. Participants underwent a 4-hour face-to-face assessment that included an interview, blood collection, physical examination and written questionnaires. Diagnoses of depressive and anxiety disorders were established with the Composite International Diagnostic Interview (CIDI version 2.1) (49). The full details of NESDA’s rationale, methods and sample have been described in a design paper (50). This thesis includes data from the baseline assessment.

The Coronary Artery Risk Development in Young Adults Study (CARDIA) is an ongoing observational cohort study that aims to identify determinants of the development of (sub)clinical cardiovascular diseases and its risk factors. Between 1985 to 1986, CARDIA performed community-based recruitment of 5,115 participants in Birmingham (Alabama), Chicago (Illinois), Minneapolis (Minnesota) and from the membership of a prepaid health care plan in Oakland (California). The study sample was balanced by race, sex and education. Follow-up examinations were conducted at years 2, 5, 7, 10, 15, 20, and 25. The majority of the baseline sample has been retained at the follow-up assessments (90%, 86%, 81%, 79%, 72%, 72%, and 72%, respectively). CARDIA participants underwent assessments that included an interview, blood collection, physical examination and written questionnaires. These included the Center for Epidemiologic Studies Depression (CES-D) scale as a measure of depressive symptoms (51). Full details of the study design, recruitment and assessment procedures have been published in a design paper (52). This thesis includes data from the assessments at years 10, 15 and 20.

Oxidative stress and antioxidant markers in this thesis
There are dozens of markers available relating to oxidative stress and antioxidants. Studies in this thesis focus on two well-established makers of oxidative damage and two important antioxidants, and have been measured in plasma or serum samples.

Oxidative damage markers
8-hydroxy-2-deoxyguanosine (8-OHdG)
8-OHdG is an oxidized product of the guanine base and one of the most abundant and widely studied free radical induced DNA lesions. 8-OHdG was first described in 1984 by Kasai et al.(53) and has since been studied in relation to exposure to exogenous sources of ROS and to the presence and development of disease. It has been investigated especially in relation to cancer owing to the fact that 8-OHdG is a DNA lesion with mutagenic potential (54,55), but also in cardiovascular disease (56).
Carotenoids

Carotenoids owe their potent antioxidant action to their ability to quench ROS (65). This property may explain why higher carotenoid levels are associated with reduced risks of metabolic syndrome (66, 67), diabetes mellitus (68–70), cardiovascular disease (71, 72) and cancer (73). In humans, the most important carotenoids include α- and β-carotene, lycopene, zeaxanthin/lutein and β-cryptoxanthin. As highly lipophilic molecules they are located in the lipid-bilayer of the cell membrane where they protect against lipid peroxidation (74). Diet is the sole source of carotenoids for mammals. Carotenoids are present in many (but not all) foods with orange, yellow or red colours such as carrots, mangos and tomatoes, and are also found in kale and spinach.

Methods for determining 8-OHdG and F2-isoprostanes

There are two main methods for determining 8-OHdG and F2-isoprostanes in tissues or body fluid samples; indirectly through immuno-assay techniques (ELISA [Enzyme-Linked Immuno Sorbent Assay]) or directly using gas or liquid chromatography coupled to electro-detection or (tandem) mass-spectrometry. The former is simpler and cheaper to perform with commercially available kits but is not considered as reliable as the gold standard method of chromatography with mass-spectrometry (60–62). Both markers can be measured either in a specific tissue or cell type (e.g. liver tissue or leukocytes) or in urine or plasma, reflecting ‘whole body’ levels of oxidative stress. Finally, it should also be kept in mind that products of oxidative damage in urine or plasma may not only reflect the levels of oxidative damage, but also of the rate of repair of this damage.

Non-enzymatic antioxidants

Uric acid

Uric acid contributes to over half of plasma antioxidant capacity (63) as a free-radical scavenger. It is the end-product of purine metabolism, which breaks down the nucleosides adenosine and guanosine and is best known for its central role in the pathophysiology of gout. It may be a particularly important central nervous system (CNS) antioxidant, owing to its stabilizing effect on a second important antioxidant, ascorbic acid, which is abundant in neurons (64). As a possible CNS antioxidant, uric acid may be of significant importance in depression and anxiety disorders.

F2-isoprostanes

F2-isoprostanes are currently considered to be the most representative marker of oxidative lipid damage. F2-isoprostanes are products of oxidation of arachidonic acid. They are prostaglandin-like compounds, but contrary to the prostaglandins they are specific products of oxidative stress. They are chemically stable and measurable in all tissues and body fluids, making them suitable and reliable markers (57). Increased levels of F2-isoprostanes have been demonstrated in atherosclerotic plaques and F2-isoprostanes maybe active contributors to the pathophysiology of atherosclerosis (58). The have been studied in a wide range of diseases, especially in cardiovascular disease and its risk factors (59).

OUTLINE

Sociodemographic, health and lifestyle determinants of oxidative stress

Chapter 2 explores the cross-sectional association of 8-OHdG and F2-isoprostanes with lifestyle factors and health indicators in a subsample of the NESDA cohort without current psychopathology. We hypothesized that poor lifestyle and the presence of disease would be associated with higher oxidative damage.

The association between oxidative stress and depressive and anxiety disorders

Cross-sectional associations

Chapters 3–6 focus on the main objective, the association between oxidative stress and depression and anxiety disorders. Chapter 3 summarizes the (then) current evidence for oxidative stress in depressive disorders. It comprises a systematic review and meta-analysis of the literature on 8-OHdG and F2-isoprostanes in depression.

Chapter 4 examines associations between oxidative damage markers, 8-OHdG and F2-isoprostanes, and depression and anxiety disorders in the NESDA cohort. In addition, this chapter focusses on whether this association is independent of antidepressant use. Chapter 5 covers the association between antioxidant uric acid and depression and anxiety disorders, also in the NESDA cohort.

Chapter 6 explores the association of the antioxidant carotenoids and oxidative damage marker F2-isoprostanes with depressive symptoms in the CARDIA cohort. Also this chapter investigates whether, and which, health and lifestyle factors explain (part of) this association.
Longitudinal associations

Chapters 4 & 6 include analyses on the longitudinal association between oxidative stress and depression and/or anxiety disorders. Chapter 4 investigates whether baseline oxidative stress predicts chronicity of symptoms or remission a two year follow-up in subjects with depressive and anxiety disorders. Chapter 6 explores the direction of the association between oxidative stress and depressive symptoms in the CARDIA cohort. Longitudinal analyses are conducted to ascertain whether depressive symptoms predict oxidative stress/antioxidant markers in the future, or vice versa.

The association between oxidative stress and physiological stress-systems

Chapter 7 investigates whether oxidative stress is related to other physiological stress systems that are known to be involved the development of somatic and psychiatric disease. In this chapter the cross-sectional associations of 8-OHdG and F2-Iso prostanes with markers of inflammation, the hypothalamic-pituitary-adrenal axis and autonomic nervous system are explored in the NESDA cohort. The expectation was that increased activity of each of these stress systems would be associated with higher oxidative damage. In addition possible interactions with the presence of psychopathology are explored.

Summary, discussion and conclusion

Chapter 8 summarizes and discusses the main findings of this thesis. The possible methodological limitations described, as well as the clinical implications of the findings and recommendations for future research.

Figure 1.1 Overview of associations by chapter.

Numbers correspond with chapters in which the associations are addressed.

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Chapter one


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