CHAPTER 1

General Introduction
THE BLACK DOG: A PERSONAL ACCOUNT OF DEPRESSION AND ANXIETY

“I have two black dogs. Sometimes I only have one. But once I see him, I know the other
one will shortly follow. I don’t always have the black dogs with me. Some days I feel
completely weightless, like I’m not carrying a burden. I’m so used to the black dogs being
around. I feel guilty not having them. I worry if they are not with me they are with
someone else. But when they are there I want them to leave. I wish they would die and
never return. But they cannot be killed.

The black dogs names are depression and anxiety. You never know when they are going
to come back to their master. Although I am their master I have no control over them.
They are constantly barking. Confusing me. I can’t think with them barking so loudly.
The shame of owning these black dogs is real. You feel like they are a sign of weakness.
You don’t want anyone knowing you have these black dogs. Especially dogs you can’t
control. When you see friends, you put the music on loud, so they can’t hear the black
dogs. You pull the curtain so they can’t see the black dogs. You’re so busy worrying about
people seeing the black dogs, so worried the black dogs will escape and bite someone that
you give up trying. You isolate yourself, wanting to be alone with them.

The dogs soon take over everything in your life. They take up all your time. People who
come over, you push away because you don’t want them to see the real side of you, the
pain and shame you are feeling. If people see the dogs get defensive. You reassure people
that “that they are OK” and “I have them trained and under control”. But you (alone) can
never get control over them.

All the things you used to enjoy are now pointless. The dogs distract you and ruin
everything surrounding you. You don’t want anyone to be affect by you having the dogs.
This is why you hide. When you finally admit to yourself that you need to get a trainer to
help train the black dogs, they leave. You think the worst is over. They won’t come back.
But (for me) they always come back. They can come back at any time and who knows, the
dogs maybe bigger and more viscous next time.

Some days I just want to end it all, I have tried once, but luckily it was unsuccessful. I just
want to have a day without the black dogs, or a day when I can fully control them. I am
glad I am now getting help, because every day it is getting better, and I am beginning to
see a light at the end of the tunnel.”

Copyright © 2018 Beyond Blue Ltd

Source:
personal-stories/story/steph
DEPRESSION

Epidemiology and burden

Mental health problems present a considerable global problem. An estimated 322 million people (4.4% of the global population) suffered from depression in 2015. The prevalence in the Netherlands is comparable, with 4.7% suffering from depression. Women have a two-fold increased risk of depression compared to men. Given that depression affects how an individual thinks, feels and acts, it is not surprising that depression was the 5th leading cause of years lived with disability in 2016. The impact of depression for an individual is also large. This is partially because depression often has a chronic-recurrent course. In specialised mental healthcare settings 60% has a recurrence after 5 years, 67% after 10 years and 85% after 15 years, and in the general population 35% has been found to have a recurrent episode after 15 years. Additionally, depression is a disorder that frequently starts during late adolescence, thereby resulting in many years of suffering. Furthermore, depression impairs physical functioning and is associated with poor somatic health.

Diagnostic criteria and treatment

From a clinical perspective depression (a major depressive disorder (MDD)) is a serious mental illness characterized by a persistent feeling of sadness and loss of interest which affects how individuals think, feel and act. According to the Diagnostic and Statistical Manual of Mental Disorders published in 2013 (DSM-V), an individual is suffering from MDD when they have five or more depressive symptoms during the largest part of the day for at least two consecutive weeks and at least one of the symptoms must be either (1) the presence of a depressed mood or (2) a loss of interest or pleasure. The remaining symptoms are: 1) increase/decrease in appetite/weight, 2) insomnia /hypersomnia, 3) psychomotor agitation/retardation 4) fatigue or loss of energy, 5) feelings of worthlessness or excessive inappropriate guilt, 6) diminished ability to think/concentration or indecisiveness, 7) recurrent thoughts of death and suicide ideation. In order to be classified as MDD, these symptoms must cause clinically significant distress or impairment in social, occupational or other important areas of social functioning and must not be attributable to the
psychological effects of a substance or another medical condition. Sometimes the depressive disorder may take on a milder but more chronic form (lasting at least 2 years). This condition is known as dysthymia. Throughout this thesis, the term depression is used in its broadest meaning including both elevated self-reported symptoms and clinical depression. When referring specifically to a clinical diagnosis of depression the term MDD will be used.

The primary treatment for MDD is antidepressants. The most important classes of antidepressants are the selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine oxidase A (RIMAs), tetracyclic antidepressants (TeCAs), and noradrenergic and specific serotonergic antidepressant (NaSSAs). As with many pharmaceuticals, antidepressants can have side effects, one of which is weight gain. Therapies, such as cognitive behavioural therapy and interpersonal therapy are also effective treatments for depression which are offered in conjunction with or as an alternative to pharmaceutical treatment. In addition to these more formal treatments, other alternative therapies such as running therapy and light therapy have been shown to have some effectiveness in reducing depressive symptoms.

Comorbidity with anxiety

MDD frequently co-occurs with anxiety disorders. Roughly 50-60% of individuals with a lifetime history of MDD report a lifetime history of one or more anxiety disorders, with the anxiety disorder generally preceding the MDD. The most common anxiety disorders comprise generalized anxiety disorder (GAD), social phobia, and panic disorder with and without agoraphobia. GAD encompasses feelings of anxiety and excessive worry about everyday situations. Social phobia is marked and persistent fear of social or performance situations where the individual fears doing something that is embarrassing or humiliating. A panic disorder is characterized by recurrent unexpected panic attacks, which may or not be accompanied by agoraphobia, the intense fear of being alone in public places with the inability to escape.
Heterogeneity of depression

Depression is a heterogeneous disorder with phenotypical symptoms varying greatly among patients. Given that a diagnosis of MDD requires five from nine remaining criteria, most of which are multi-dimensional, there are 227 unique symptom profiles that could potentially exist to qualify for a diagnosis of MDD. The clustering of specific symptoms has led to the classification of depression subtypes. One of the most commonly explored symptom-based subtypes are melancholic depression and atypical depression. Melancholic depression is characterized by a depressed mood that is not reactive to circumstances, exhibiting typical vegetative symptoms including early morning wakening, diurnal variation with worse mood in the morning and weight loss. Conversely, atypical depression is characterized by a mood reactivity (i.e. mood brightening in response to positive events), overeating or weight gain, oversleeping, leaden paralysis and interpersonal rejection sensitivity. Depression is also heterogenic in terms of its polarity (unipolar (i.e. MDD) vs. bipolar (MDD with manic episodes), onset (specific events, seasons, or age), recurrence, and severity.

Factors related to depression

Depression does not have a single cause and there are many factors which may contribute to an individual developing a depressive episode. For example, stressful events such as the death of a close friend or relative or the loss a job may trigger a depressive episode. Alternatively, certain psychological conditions such as negative patterns of thinking can increase the risk of developing depression or a physical ailment such as diabetes mellitus type 2 or cardiovascular disease has also been associated with depression. Recent literature has also shown evidence for the existence of a genetic predisposition for depression and anxiety disorders. However, as many other factors have also been proposed as causing, or at least increasing the risk of, depression, we can conclude that the cause of depression is “multifactorial”.

These factors are sometimes clustered into biological, psychological and social domains, which is illustrated in the biopsychosocial model developed by cardiologist Dr. George Engel. This model suggests that biological, psychological and social factors are all
interlinked and play an important role with regard to promoting health or causing disease (Figure 1). Thus, in order to understand how a depressive episode may arise, it is important to consider the complexity and interdependency of the associated risk factors.

Two factors which have been longitudinally associated with the development of depression are obesity\textsuperscript{19} and dietary intake.\textsuperscript{20} These will form the basis of this thesis.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{biopsychosocial_model.png}
\caption{Biopsychosocial model of mental health (adapted from londonscientificneurotherapy.com)}
\end{figure}
OVERWEIGHT AND OBESITY

Overweight and obesity are usually defined in terms the body mass index (BMI), body weight in relation to height. The most frequently used cutoffs are a BMI $\geq 25$kg/m$^2$ to $< 30$kg/m$^2$ for overweight and BMI $\geq 30$kg/m$^2$ for obesity.\textsuperscript{21} Obesity and overweight combined affect over a third of the world's population today\textsuperscript{22,23} and if current trends continue, an estimated 38% of the world's population will be overweight and a further 20% will be obese by 2030.\textsuperscript{24}

There is strong epidemiological evidence that obesity and depression are not independent of each other. Cross-sectional studies have shown that those with obesity have a 23-41% increased risk of also suffering from depression based on self-reported symptoms and 14-30% increased risk based on a clinical diagnosis.\textsuperscript{25} Longitudinally, a meta-analysis has shown a temporal relationship with obesity increasing the risk of developing depression.\textsuperscript{25} However, the association between obesity and depression is not necessarily unidirectional, and some studies have suggested a bidirectional link.\textsuperscript{19} Given that an unintentional change in weight is a symptom of depression and changes in behavior, such as a reduction in physical activity is also associated with depression onset, a bidirectional link is plausible.

Generally most studies show a dose response relationship between BMI and depression, with higher BMI's showing greater risks of developing depression. However, a linear relationship is mostly evident when comparing overweight, obese and extreme obese person to normal weight. Some studies have also shown that being underweight is also associated with depression.\textsuperscript{26,27}

Obesity is characterized by an increase in white adipose tissue, the organ with which the buffering of energy intake is rendered. This organ also has an endocrine function and is the primary source of leptin, a hormone that regulates appetite, and a number of other adipokines involved in metabolic and physiological processes. Some of these proteins, such as tumor necrosis factor alpha (TNF-$\alpha$) and interleukin 6 (IL-6), are inflammatory cytokines. Circulatory levels of these factors are increased in an obese person, leading obesity to be termed as a state of chronic, low-grade inflammation.\textsuperscript{28} Prolonged inflammatory activity can promote neuroinflammatory responses and depressive
behavior. However, this is not the only manner in which obesity may promote depression. In addition to inflammation, three other biological pathways have been proposed, leptin/insulin resistance, long-term hypothalamic–pituitary–adrenal axis (HPA-axis) hyperactivation and shared genetic risk. Leptin, a hormone which controls appetite and hunger, has antidepressant like effects in the brain, thus resistance to this hormone could result in weight gain and poorer mood. Obesity increases the risk of insulin resistance resulting in disturbed glucose metabolism and ultimately diabetes type 2. Insulin receptors have been found in the brain particularly in the hippocampus and limbic structure. This may explain why insulin resistance has been associated with executive function impairments and neuronal damage which are thought to play a role in depression. Hyperactivation of the HPA-axis results in an abundant release in cortisol, which is a consistent finding in people with depression. Excessive cortisol can lead to neurological damage and atrophy in the hippocampus and increases appetite potentially leading to obesity. Finally, recent literature has suggested a shared genetic risk between obesity and depression, presumably the common genetic bases act via one of the shared biological pathways.

Alternatively, obesity may increase the risk of depression through psychological mechanisms, such as via low self-esteem or social stigma. Obese persons are more likely to suffer from increased body dissatisfaction, low self-esteem and perceived stigmatization which are hypothesized to increase the risk of psychiatric disorders and in particular, depression.

The current literature could benefit from more studies based on a clinical diagnosis of depression (i.e. MDD) as it is currently unclear as to whether the impact of obesity on depression is sufficient to result in MDD or whether it just contributes to increased depressed feelings. Other shortcomings with the current literature are the lack of adjustment for lifestyle factors and somatic comorbidities which may partially explain the relationship between obesity and depression, ignoring depression history and the inability to investigate different depression trajectories such as a chronic course. Other important areas where the current literature is limited is among cohorts using data over the lifespan, enabling analysis of data from childhood to old age, and cohorts which include a range of
ethnic minorities more typical to Europe (as opposed to the USA). Literature investigating depression and subsequent weight change generally ignores antidepressant use, which can affect appetite and body weight, and lack the ability to include those with a history of depression.

**DIETARY INTAKE**

Adequate nutrition is essential for the maintenance of the body and general health. Over the past 50 years the role of poor nutrition in preventing non-communicable diseases such as cardiovascular disease has been widely investigated. However, in the past ten years research has been broadened to consider mental health as a condition that can be influenced by nutrition.

Early research into nutrition mostly focused on individual nutrients or individual food groups such as vegetables. However, more recent research has concentrated on analysing the diet as a whole. This is because nutrients are not consumed in isolation but in the form of food items which themselves are combined together to form the whole diet. Additionally, some components act synergistically (e.g. orange juice and iron), whereas other components work in opposition (e.g. calcium and foods containing oxalic acid). The complex interactions and cumulative effects cannot be captured well by studying the effects of single nutrient or food groups. Finally, another downside of analyzing individual food components is that a change in intake of a single food component requires the assumption of a substitutional food component if the overall calorific intake is to remain the same. Thus analysis of individual food components in relationship to health cannot be made in isolation and should acknowledge the potential replacement food items. Analysing the diet as a whole overcomes these problems.

There have been many studies analyzing nutrients, food groups, dietary patterns and diet quality in relationship with depression. Among individual nutrients omega-3 polyunsaturated fatty acids, vitamin D, magnesium, folate, vitamin B6, vitamin B12, and zinc have all been found to be associated with depression in individual studies, but not in all. Food groups that have been associated with depression are fruit
and vegetables,\textsuperscript{39} fish,\textsuperscript{40} and high fiber food.\textsuperscript{41} Overall dietary analysis shows that healthier dietary patterns, or closer adherence to a predefined healthy diet score, such as the Mediterranean diet score, are associated with lower depressive symptoms and a lower risk for the onset of depression.\textsuperscript{20,42} Conversely, unhealthy diets have been associated with higher depressive symptoms.\textsuperscript{20}

Reasons why poor nutrition may potentially affect mental health is that poor nutritional intake leads to nutrient deficiencies which have a detrimental impact on biological systems that underpin the pathogenesis of depression. Alternatively, some dietary components have positive effects, such as long chain omega-3 polyunsaturated fatty acids (present in fish) which have been shown to have an anti-inflammatory effect, which may thereby positively impact on depression.\textsuperscript{43,44} Another possible explanation linking dietary intake to depression is through emotional eating, which, due to the inability to distinguish hunger from other bodily arousal (e.g. emotions), leads to increased food consumption, particularly energy-dense sweet/ high fat foods, thereby excluding healthier choices.\textsuperscript{45,46} Previous studies have confirmed an association between emotional eating and depressive symptoms.\textsuperscript{46,47} Finally, poor nutrition is generally characterised by a high energy intake, which leads to weight gain and ultimately obesity which itself is a risk factor for increased depressive symptoms. Conversely, it is also possible that being depressed is likely to lead to poorer diet quality. Reduced energy levels and motivation are typical symptoms of depression. Generally, maintaining a healthy diet with the preparation of fresh fruit and vegetables requires more energy and motivation than eating unhealthy fast food. Finally, some literature suggests that depressed persons express a preference for more palatable “comfort foods” and carbohydrate rich food, which in the short term may improve mood through increased serotonin release\textsuperscript{48,49}, but in the long term may compromise mental health and body weight.

Despite the wealth of research examining depression and diet quality few studies are conducted among clinical patients, instead relying on self-reported symptom questionnaires. Thus, most studies only can draw conclusions about depressive symptoms and not MDD. This is important as those with depressive symptoms may not necessarily be depressed as many symptoms typical to depressed persons are also caused by somatic problems.
Furthermore, these studies lack the ability to analyses clinical characteristics such as the severity and chronicity of symptoms. Another weakness is that the comorbidity with anxiety is mostly ignored. Additionally, as MDD is a heterogeneous disorder, the diversity of symptom profiles should not be ignored.

**THIS THESIS**

The main objective of this thesis is to study the associations of BMI and diet quality with major depressive disorder. In order to address the shortcomings mentioned above, this thesis will primarily use data from a cohort designed to study the development of depressive and anxiety disorders, thus allowing the analysis of the clinical characteristics and trajectories of depression in association with BMI and diet quality. The other two cohorts used are also unique in that the first allows analysis of a BMI and depression within a European ethnic minorities cohort and the second has data from birth to old age.

**Central aims**

This thesis will be divided into two parts. The first half will focus on BMI and depression and the second half will focus on diet quality and depression.

The specific aims are to establish whether:

1) a. Obesity and higher BMI are associated with an increased risk of depressed mood (cross-sectionally) and increased risk of developing depression (longitudinally).

   b. Depression is associated with subsequent changes in weight.

2) Depression is related to dietary intake (dietary quality and food groups) (cross-sectionally).

**Cohort studies in this thesis**

NESDA: The Netherlands Study of Depression and Anxiety is an ongoing observational naturalistic cohort which aims to identify the social, psychological, biological and genetic factors that determine the onset and course of depressive and anxiety disorders. It was set
up in 2004 and recruited 2,981 participants from three different settings, the community, primary care and specialized mental health care, from three different regions (Amsterdam, Groningen and Leiden areas) in the Netherlands. The baseline interviews included a medical examination, blood and saliva samples, a psychological diagnostic interview, anthropometric measurements and collection of socio-demographic, medical history and lifestyle data. The interviews were carried out by specially trained staff. Follow-up interviews were carried out after 2, 4, 6 and 9 years. The 9-year interview also included data collection of dietary intake. More details about this cohort can be found in the paper by Penninx et al.50

HELIUS: The Healthy Life in an Urban Setting (HELIUS) is a multi-ethnic cohort study conducted in Amsterdam, the Netherlands, which aims to gain insight in the biological, psychological and social causes of the unequal burden of disease across ethnic groups. Data was collected between 2011-2015 and included 22,165 participants of Dutch, Turkish, Moroccan, Ghanaian and Surinamese (African and Asian) origins aged 18-70y. Data collection included physical examinations, blood samples and questionnaires. Detailed information about the HELIUS study is found elsewhere.51

AGES-Reykjavik: The AGES-Reykjavik (Age, Gene/Environment Susceptibility) cohort (n=5764) is drawn from a random selection of survivors from the established population-based cohort, the Reykjavik Study. The Reykjavik study is a cohort of 19,381 Icelandic men and women born between 1907-1935 that were followed in their mid-life phase during 1967-1991 by the Icelandic Heart Association. The AGES-Reykjavik study was a follow-up study designed to examine risk factors, including genetic susceptibility and gene/environment interaction, in relation to disease and disability in old age. Data measurements were performed during 2002-2006 and included blood draws, electrocardiograms, anthropometry (BMI), and measures of psychological and physical function. Information about the AGES study can also be found in the paper by Harris et al.52
Outline of the thesis

A summary of the individual analysis can be found in Figure 2.

Figure 2. Schematic summary of the analyses performed in this thesis
The numbers refer to the individual chapters found in this thesis which are as follows:
2: The relationship between obesity and depressed mood in a multi-ethnic population. The HELIUS study,
3: Childhood overweight and obesity and the risk of depression across the lifespan,
4: The role of obesity measures in the development and persistence of major depressive disorder,
5: Major depressive disorder, antidepressant use, and subsequent 2-year weight change patterns in the Netherlands Study of Depression and Anxiety,
6: Diet quality in persons with and without depressive and anxiety disorders,
7: Association of food groups with depression and anxiety disorders.
Chapter 2 will explore the cross-sectional association between obesity and depressed mood in a large multi-ethnic population using data from the HELIUS study. Potentially, health behaviours such as smoking, alcohol intake and physical activity or somatic health may explain the relationship between obesity and depression. Thus, ethnic differences will be explored in different models with adjustment for sociodemographic factors, health behaviours and somatic health to explore the influence these variables have on the obesity/depression association among ethnic groups.

Chapter 3 explores the longitudinal association between BMI/obesity and MDD/depressive symptoms over the whole life-course using data from the AGES-Reykjavik study. Specifically, the association between measured BMI at two life stages in childhood (aged 8y) and early adolescence (aged 13y) with depressed mood measured at late-life (measured at age ~75y) will be investigated. Additionally, the relationship of childhood/adolescent BMI with having MDD over a lifetime (approximately 65 years of follow-up) will be examined.

Chapter 4 and 5 investigate the longitudinal relationship between BMI/waist circumference or weight change and MDD using data from NESDA. Chapter 4 examines the prospective relationship between BMI and waist circumference with the development of MDD short-term (2 years) and long-term (6-year) in participants with no current MDD at baseline. This chapter will also investigate the relationship between BMI and waist circumference with the persistence of depression over a 2-year and 6-year period, in participants who currently have MDD.

Chapter 5 focuses on whether MDD is associated with subsequent changes in body weight, both weight gain and weight loss. This chapter also investigates the use of antidepressants and its association with subsequent weight changes, both independently and in conjunction with depression status. Finally, this chapter will also explore why some depressed patients gain weight, whilst others lose weight by comparing general demographic
and health characteristics and depressive symptom profiles of those that gain versus those that lose weight.

The association of depression with diet quality and food groups

The cross-sectional relationship between depressive (MDD, dysthymia) and anxiety disorders with diet quality will be investigated in chapter 6 using NESDA data. Initially the relationship between having depressive and/or anxiety disorders and diet quality, measured using two different diet quality scores, will be assessed. Subsequently, specific clinical characteristics, namely (1) disorder type (depressive disorder, anxiety disorder and their comorbidity), (2) chronicity, and (3) disorder severity and diet quality will be explored. Finally, the relationship between individual clinical symptoms encompassing atypical and melancholic features of depressive disorder and diet quality will be explored.

Chapter 7 switches focus to individual food groups: here the association between the individual food groups associated with Mediterranean diet and depressive and anxiety (disorder and severity) will be examined. The food groups will be examined in isolation and in combination with each other in order to establish which dietary components are independently related to depression and/or anxiety and depressive or anxiety symptoms. These analyses will all be done using data from NESDA.

The final chapter provides an overview of the main findings from all studies found in this thesis along with a broader general discussion about the conclusions we can draw from these and other studies. Additionally, public health implications and recommendations for future research will also be discussed.
REFERENCES

34. Anglin, R. E. S., Samaan, Z., Walter, S. D. & McDonald, S. D. Vitamin D deficiency and depression


