CHAPTER 8

General Discussion
AIMS OF THIS THESIS

The aim of this thesis was two-fold. First, we wanted to examine the link between body mass index (BMI) and depression: whether obesity and a higher BMI are associated with an increased risk of (the development) of depression, and whether depression is associated with subsequent weight change. Secondly, we examined the cross-sectional relationship between depression and dietary intake. We did this using data from three cohorts, the Netherlands study of depression and anxiety (NESDA), the Healthy Life in an Urban Setting (HELIUS) and the AGES-Reykjavik study.

The current chapter will include a summary of the main findings from Chapters 2 to 7, a discussion of the results within the framework of existing literature, a discussion on methodological considerations, implications for clinical practice and suggestions for future research.

Main Findings

A summary of the main findings can be found in figure 1.

AIM 1A) To establish whether obesity and higher BMI are associated with an increased depressed mood (cross-sectionally) and increased risk of developing depression (longitudinally).

The three chapters (2-4) examining the association between obesity/higher BMI and clinical depression/depressed mood provide evidence that being obese or having a higher BMI is associated with depression. Cross-sectionally (chapter 2), both BMI and waist circumference revealed that the odds of having a depressed mood was 16% and 20% higher per standard deviation (SD) (corresponding to 5.3 kg/m²) higher in BMI or waist circumference, respectively. Additionally, having overweight or obesity, or a waist circumference measurement in the highest two quartiles was likewise associated with significantly higher odds of having a depressed mood. Correspondingly, when examined longitudinally (chapter 4), we found that, over a 6-year period, those with a BMI or waist circumference one SD higher had higher odds of developing a clinical depression diagnosis by 17% and 20% respectively, although obesity and a waist circumference...
Figure 1. Schematic summary of results
Abbreviations: BMI=body mass index, WC=waist circumference, SD=standard deviation, MDD=major depressive disorder, PHQ-9=Patient health questionnaire 9 items, GDS=geriatric depression scale, MDS=Mediterranean diet score, AHEI=Alternative healthy eating index

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Analysis</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| 2       | Cross-sectional | Depressed mood
|         | Longitudinal | Lifetime MDD, Development of MDD, Late-life depressive symptoms
| 3, 4    | Longitudinal | Persistence of MDD
| 5       | Longitudinal | Comorbid depression & anxiety disorder
| 6, 7    | Cross-sectional | Associated with lower risk of weight gain (2 & 6 yrs), weight loss (2 years)

1PHQ-9 ≥10
2GDS≥25
measurement in the highest quintiles were not significantly associated with the development of depression. However, over a 2-year period the association of BMI and the development of depression was weaker. Analysis of childhood (age 8y) overweight and obesity suggests that the relationship between unhealthy weight and the increased risk of lifetime depression starts during childhood (chapter 3).

AIM 1B) To establish whether depression is associated with subsequent changes in weight

The analysis detailed in chapter 5 found two main results. Firstly, persons with current MDD have a 67% higher odds of gaining more than 5% over their body weight over a 2-year period than remaining stable in their weight, compared to controls. Secondly, persons with current depression also have a higher risk (27%) of losing at least 5% of their body weight than remaining weight stable compared to controls. This relationship remained after allowing for antidepressant use.

AIM 2) To establish whether depression (and anxiety) disorders are related to dietary intake.

Our analysis shows that depressive and/or anxiety disorders were significantly associated with poorer diet quality (chapter 6). Subsequent analysis showed that this was particularly true for those that had comorbid anxiety and depression. Further examination of clinical characteristics showed that both the chronicity (measured in % months with elevated depressive symptoms over a 9-year period) and the severity of the depression/anxiety disorder had a dose response relationship with diet quality, thus the more chronic/severe the disorder the poorer the quality of diet. When instead of a combined diet score, individual food groups that contribute to a healthy diet score were analysed, using food groups as the determinant (chapter 7), it appeared that increased consumption of non-refined grains was associated with lower odds of having current depression/anxiety diagnosis and greater consumption of both non-refined grains and vegetables was related to lower depressive and anxiety symptoms. Higher overall energy intake was significantly associated with higher anxiety symptoms. The association between non-refined grains and depression/anxiety (diagnosis and symptoms) remained significant even when allowing
for the consumption of other food groups. However, as the combined diet score showed the strongest relationship with depression and anxiety (symptoms and diagnosis), we can conclude that it is the synergistic impact of the whole diet that has the greatest association with depression/anxiety.

**DISCUSSION OF THE MAIN FINDINGS**

**BMI/obesity and risk of depression**

Our findings that BMI/obesity is bidirectionally associated with depression are confirmed by those of both cross-sectional and longitudinal meta-analyses.\(^1\)\(^-\)\(^6\) We also found evidence that being obese or overweight (but not BMI as a continuous measure) at a child age 8 is associated with an increased risk of having life time MDD, thus tentatively indicating that the obesity-depression association starts as early as childhood. This too is in line with the existing literature.\(^7\)

However, our results did raise some other issues. Firstly, as evidenced by our analysis using data from the Dutch HELIUS study and confirmed by studies in the United States of America, this relationship is not consistent across all ethnic groups. According to our results, only the native white Dutch population and the African Surinamese showed a significant relationship between being obese or having a waist circumference in the highest quartile and depressed mood. These ethnic differences were consistent for both genders and across all age groups. This leads us to the possibility that there may also be other categories of people for whom higher BMI is not necessarily related to depression. One possible distinguishing category by which persons could be subdivided would be gender. Two meta-analyses found that the obesity-depression relationship is stronger in women compared to men, however this was only observed in cross-sectional studies.\(^1,4,5\) We found no differences between men and women in the two studies where data was sufficient to allow testing of interaction terms, which is in-line with a meta-analysis of longitudinal studies.\(^5\) Age is another possible factor which may influence whether obesity is associated with depression. A couple of studies found that BMI is more relevant to increased depression in a younger population.\(^8,9\), although this was not confirm this
within NESDA and HELIUS. This is perhaps also reflected in our finding that childhood overweight and obesity are a risk factor for MDD over a lifetime. However, according to our results being overweight or obese during childhood/early adolescence is not associated with depressive symptoms during late-life (±75 years). Possibly, other, more important factors contribute to depressive symptoms during late-life, for example chronic diseases, frailty, poor physical functioning and sleep disturbances.

Secondly, our results showed that longitudinally, BMI and waist circumference were only related to the development of MDD over a 6-year period and not over a 2-year period. Not only was the association between obesity measures and MDD non-significant over the 2-year period but it was also a weaker relationship compared to over a 6-year period (chapter 4). A previous meta-analysis has also noted that the association between BMI and depression is stronger for studies with a longer follow-up. Possibly, the duration of exposure to obesity is of relevance to the development of depression, or alternatively, a longer time period is needed to impact on a psychiatric diagnosis.

Thirdly, although there is evidence that higher BMI and waist circumferences lead to the development of depression, we found no evidence that higher BMI and waist circumference is associated with the persistence of depression over either a 2 or 6-year period (chapter 4). This is contradictory to the only other study that examined consistent obesity and persistence of depression, although this study was performed in adolescents and not adults. This study concluded that the relationship between obesity and continuous depression was due to poor physical health. Possibly, BMI only plays a role in the development MDD and not in the persistence of MDD.

**Role of Lifestyle and Comorbidity**

All three of the papers investigating obesity measures and the risk of depression included adjustments for possible confounding variables. These were grouped into socio-demographic variables (age, sex & education) and lifestyle variables (smoking behavior, alcohol use and physical activity). Two papers were also able to include chronic diseases. Potentially, lifestyle variables and comorbidities (chronic diseases) could lie on the causal
path between obesity and depression which would lead to an underestimation of the true association after adjustments. However, in both the cross-sectional analysis and longitudinal analysis these variables had little impact on the effect sizes, indicating that these factors are unlikely to be strong mechanisms. Other possible mechanisms such as immune-inflammatory activation, leptin resistance and microbiome alterations, body dissatisfaction and stigmatisation are discussed below.

**Depression and subsequent weight change**

We found that persons with MDD have a significantly greater odds of gaining or losing weight over a 2-year period compared to healthy controls. These findings are in line with those of other studies.\textsuperscript{11–15} All of these studies found that depression leads to weight gain, and three also found an association between depression and weight loss.\textsuperscript{11,13,14} Compared to these other studies we found stronger associations (odds ratios) between weight change and depression which is probably attributable to the fact that in a psychiatric cohort, on which these analyses were based, we included more severe cases of MDD.

The association between depression and weight gain was still evident after a 6-year period, although not for weight loss. Given that the majority of patients with MDD recover within the 6-year period we could assume that weight loss is a short-term phenomenon associated with the acute phase of MDD. Weight gain however, persists, maybe due to the know difficulties in trying to lose weight.

Not only did we find that depression leads to weight gain, but this appeared to be independent of antidepressant use. Various antidepressants have been associated with weight gain including tricyclic antidepressants (TCAs)\textsuperscript{16,17}, some selective serotonin reuptake inhibitors\textsuperscript{18}, mirtazapine\textsuperscript{16} and venlafaxine\textsuperscript{16}. We did not find an association between TCA use and weight gain. More importantly, combining both antidepressant use and depression status into one model showed that being currently depressed remained significantly associated with both weight loss and weight gain, thereby suggesting that weight gain cannot be solely attributed to antidepressant use. Congruent with our results a meta-analysis examining body weight changes due to antidepressants concluded that most
antidepressants have transient and negligible effects on the body in the short term (4-12 weeks).\textsuperscript{19}

**Depression and Anxiety and dietary intake**

Our results showed that depression and/or anxiety disorders were significantly related to poorer diet quality. Most other cross-sectional studies look at the association between diet quality and depression, thus in the other direction. These studies have shown mixed results. Although many studies confirm our finding of an association between diet quality and depression,\textsuperscript{20–26} a few studies find no association.\textsuperscript{27–29} Congruent with our results, vegetable consumption has been consistently associated with depression when analysed in conjunction with multiple food groups,\textsuperscript{30–33} as well as in studies focusing on vegetable consumption alone.\textsuperscript{34,35} The relationship between non-refined grains and depression has only been examined twice previously, these studies were in line with our results.\textsuperscript{32,36}

Although we only analysed the cross-sectional relationship between depression and diet quality, there are also many studies that have examined the longitudinal relationship with the assumption that poorer diet quality can lead to the development of depression. A couple meta-analyses have provided evidence that a higher quality of diet is associated with a lower risk for the onset of depression.\textsuperscript{34,37}

There are no longitudinal studies that investigate whether the development of depression can lead to a poorer diet, although there are plausible explanations as to why a depressed person may adopt more unhealthy eating habits. Firstly, as a change in appetite is one of the possible symptoms of depression according to the DSM-IV, it is fair to assume that this may lead to a change in dietary habits. Additionally, depressed persons typically have reduced motivation and energy. Healthy food usually requires more effort to prepare, whereas unhealthy fast food is quick and easy to access, thereby requiring less energy to prepare. Thus, depression may lead to a reduced dietary quality.
POTENTIAL MECHANISMS

Mechanisms linking obesity and depression

Plausible mechanisms which may explain a link between obesity and depression are diverse, ranging from biological aspects, psychological factors and social factors. Genome wide association studies (GWAS) have identified a possible shared genetic risk for obesity and depression. A recent meta-analysis of GWAS studies based in 135,458 cases and 344,901 controls identified 44 independent and significant loci associated with MDD. Two of these loci have single nucleotide polymorphisms (SNP’s) located or near them which have previously associated with obesity and body mass index. Subsequent Mendelian randomisation used to investigate the relationship between MDD and BMI provided evidence for a 1.12-fold increase in major depression per standard deviation of BMI and there was no evidence for reverse causality.

On a physiological level, obesity has been shown to involve dysregulation of the hypothalamic-pituitary-adrenal axis (HPA-axis) activation, immune-inflammatory activation, leptin resistance and microbiome alterations. Hyperactivation of the HPA-axis is a feature common to both obese and depressed people. The resulting abundance of cortisol leads to neurological damage and impairment of the hippocampus and amygdala which is associated with depression. A long-term increase in cortisol results in increased appetite, with a preference for energy rich food, promotes adipogenesis and hypertrophy of visceral fat and suppresses thermogenesis. Thus, there is evidence that hyperactivation of the HPA-axis could potentially be responsible for both depression and obesity or weight gain.

Alternatively, resistance to leptin and leptin insufficiency, a characteristic of obesity, may constitute a risk for depression. Leptin is a hormone produced in proportion to fat mass, which controls appetite and energy expenditure. Leptin resistance occurs when the transport of leptin across the blood–brain barrier is impaired, which reduces the function of leptin receptors, and causes defects in leptin signal transduction. Leptin also has an impact on mood. Animal models have shown that peripheral and central administration
of leptin produces antidepressant-like effects.\textsuperscript{43} Interestingly, among currently depressed patients, higher leptin levels have been associated with key symptoms identifying the atypical depressive subtypes, such as hyperphagia, increased weight, and leaden paralysis.\textsuperscript{44} Given that higher leptin levels were not associated with MDD overall would suggest that leptin resistance is a mechanism specific to atypical depression.

The fact that obese individuals display basal low-grade inflammation and enhanced susceptibility to immune-mediated diseases has lead obesity to be termed an inflammatory condition affecting both innate and acquired immunity.\textsuperscript{45} Increased plasma levels of cytokines including interleukin (IL)1\textbeta, tumor necrosis factor (TNF)-\textalpha, IL-6 and C-reactive protein have all been reported in obese individuals. White adipose tissue (fat tissue), especially in the abdominal area and muscles (ectopic fat), is an active endocrine organ which produces these inflammatory cytokines.\textsuperscript{46} Depressed subjects exhibit significantly higher levels of these inflammatory markers.\textsuperscript{47,48} It is thought that the peripheral immune activation can be translated into central inflammation in the brain. Central inflammation impacts on established pathophysiological processes of depression, such as monoaminergic neurotransmission alteration.\textsuperscript{45} Furthermore, cytokines influence HPA-activation by disrupting the negative feedback circuit, illustrating that the two mechanisms are linked to each other.\textsuperscript{49}

Observational evidence has confirmed an association between type 2 diabetes mellitus and depression,\textsuperscript{50,51} leading to the proposal that insulin resistance may also play a role in depression. Obesity increases the risk of insulin resistance, a state in which tissues becomes unresponsive to insulin. It is thought that the increased levels of pro-inflammatory cytokines arising from the obesity related inflammation, disable insulin receptors thereby inhibiting downstream signaling. Insulin receptors are also found in the brain, particularly in the hypothalamus and limbic regions. Available animal and human experiments have suggested that insulin has mood-enhancing effects.\textsuperscript{52,53} More recent research has explored the role of the microbiota in the gut as a potential mechanism linking obesity with depressive symptoms. Obese subjects have been found to have an impaired ratio of Bacteroidetes/Firmicutes. These alterations are also related to markers of local inflammation which result in increased gut permeability. This contributes
to the onset and progression of systemic inflammation which is thought ultimately to trigger depressed mood.\textsuperscript{42}

Emerging evidence has suggested that there is a clustering of biological dysregulations according to specific depressive subtypes. According to one study which used latent class analysis to distinguish subtypes,\textsuperscript{54} HPA-axis hyperactivity tends to be a feature of persons with melancholic depression, whilst metabolic disturbances and inflammation are characteristics of atypical depression. Thus the heterogeneity of depression due to differing symptom presentation is also expressed in differing biological pathways. Furthermore, it has been suggested that the co-occurrence of obesity and depression is a factor more predominant in atypical depression as those with atypical symptoms tend to have higher BMI’s.\textsuperscript{55}

Alternatively, there are psychological factors which could explain the association between obesity and depression. Persons with obesity frequently suffer from increased body dissatisfaction which can lead to lower self-esteem, which itself can lead to depressive symptoms.\textsuperscript{56} Body dissatisfaction and self-esteem are not however, universal in all obese subjects and potentially varies according to cultural norms, gender and age. For example, we would expect body dissatisfaction to be greater during adolescence when appearances and peer approval are key values. This has been suggested by one study that found the correlation between BMI and self-esteem is strongest up until age 32 and is diminished by age 42.\textsuperscript{57} Body dissatisfaction may also differ between ethnic groups as one meta-analysis performed on U.S. female subjects suggests that ethnic differences in body dissatisfaction are minor.\textsuperscript{58} Although the European ethnic groups differ from those in the U.S., this does suggest that body dissatisfaction may not necessarily be a universal mechanism among persons of different ethnicities.

Finally there are social factors which may explain why obese persons are more likely to suffer from depressive symptoms. Obese people are frequently stigmatised and suffer from discrimination due to their weight. This potentially leads to increased psychological stress and the development of depression.\textsuperscript{59} Perceived weight discrimination is not universal and has been found to differ among different cultures and between men and
women. Stigmatisation can be a particular problem during childhood where overweight and obese children are subject to bullying. Stigmatisation and bullying lead to psychological stress, which is a contributing factor to the development of depression.

In summary, there are many possible mechanisms that could explain the association between obesity and depression: biological, psychological and social mechanisms. Most likely not one single mechanism is involved, mechanisms could be interrelated. Furthermore, theoretically, there are mechanisms which can explain the pathways in both directions (i.e. that obesity can lead to the development of depression and vice versa), however recent research using Mendelian randomisation suggests that there is evidence for a causal, increasing effect of BMI on depressive symptoms but no evidence for causality in the other direction. Although we did not analyse whether depression can promote the development of obesity, we did find that those who subsequently gained weight over a 2-year period had lower starting BMI’s compared to those who lost weight. Furthermore, those who gained weight were more likely to report weight loss and a loss of appetite as symptoms of depression. Thus our results suggest long-term changes in weight reflect a rebalancing of the changes experienced during the acute phase of depression.

Mechanisms between dietary intake and depression

The association between the dietary quality and depression/anxiety is complex and arguments can be made for a bidirectional relationship. An explanation as to why those suffering from MDD may have poorer diet quality is that depressive symptoms frequently preclude healthy behaviours. Two symptoms that are directly linked to diets are poor (or increased) appetite and weight loss (or gain). Furthermore, depressed persons commonly suffer from a loss of motivation and a lack of energy. Given that healthy diets typically require more time and cooking skills, whereas unhealthy foods are quick and easy to prepare, it would not be surprising that depression leads to poorer diet quality. This pathway could also explain why depression may lead to weight gain. As well as a poorer quality of diet, depression also influences other unhealthy behaviours such as less physical

General discussion
activity, alcohol abuse and smoking. Some of these unhealthy lifestyle behaviours can also facilitate weight gain.

Alternatively, depression could influence food choices through the HPA-axis, which, as previously mentioned, is hyperactive in people with depression. Elevated activity of the HPA-axis is paired with an increase in serum glucocorticoids which stimulate an increase in appetite with a preference for energy rich foods, probably at the expense of healthier food.

Many of the proposed pathways explaining the link between depression and diet quality describe how a less healthy diet leads to an increase risk for the development of depression. These possible mechanisms include both direct pathways, such as deficiencies or abundance of nutrients important to mental health, or indirectly by affecting the gut microbiome, via obesity or poor metabolic health.

Poor diet quality can result in deficiencies in certain vitamins and minerals which could impact depression directly by influencing biological pathways associated with the pathophysiology of depression. One such vitamin is folic acid which is abundant in vegetables, whole grain products, meat and dairy products. Low levels of folic acid have been associated with depression. Folate, a derivative of folic acid, is involved in the metabolism of monoamines, such as serotonin, in the brain. Serotonin insufficiencies have long been believed to cause depressive like symptoms. Zinc is a mineral found in, among other things, whole grain products. Zinc deficiencies result in a comparative reduction in synaptic zinc, which can increase the glutamatergic level by the activation of N-methyl-D-aspartate receptors, which is associated with depression. Additionally, decreased synaptic zinc levels can also affect brain derived neurotrophic factor activity which is also involved in depression. Other potentially important nutrients are copper and magnesium, which are found in wholegrain products, vitamin B12, found in meat, fish and dairy products, and B6 vitamins, found in meat, fish, dairy, legumes and wholegrain products. All of these vitamins are necessary for the production of neurotransmitters and thus a potential link to mental health.
Conversely a healthy diet, such as the Mediterranean diet, which is abundant in fruit, vegetables, fish and wholegrain products, has a positive effect on physiological and mental health. The Mediterranean diet is associated with increased circulating levels of plasma antioxidants and decreased oxidative stress. Anti-oxidants counteract free radicals and may therefore help alleviate oxidative stress, which has been shown to be increased in depressed persons.

The Mediterranean diet has also been associated with a reduction in inflammation markers, elevated levels of which are a characteristic of depression. The mechanism behind this association may be through the dietary influences on the gut microbiome. In adults, diets that have a high proportion of fruit and vegetables and a low consumption of meat are associated with a highly diverse microbiota whereas the reverse is true for diets low in plant based food. One study has proposed that changes in gut flora ratios are important in determining the pro- or anti-inflammatory balance in the gut. Animal experiments have shown that intestinal permeability is affected by the gut flora profile and an increase in gut permeability is associated with an increase in circulating bacteria-derived lipopolysaccharide (LPS), which triggers both an immunological and inflammatory response. Diets high in lipids has also been shown to promote increased intestinal permeability. Another mechanism by which the Mediterranean diet may influence inflammation is through omega-3 polyunsaturated fatty acids (PUFAs), which are found predominantly in fish and shell fish. Long chain omega-3 PUFAs, docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA) and their derivatives, are well-known regulators of the inflammatory response and have recently been shown to also regulate neuroinflammatory processes. This is corroborated by the fact that depressed persons seem to have lower circulating omega-3 PUFAs than healthy persons. Furthermore, omega-3 PUFA influence the HPA axis by lowering cortisol levels.

Alternatively, diet and depression maybe linked indirectly through poor metabolic health and chronic diseases, which in turn poses a risk for depression. Several chronic diseases have been associated with depression, many of which, such as cardiovascular disease, are exacerbated by an unhealthy diet. Unhealthy diets also increase the risk of metabolic
diseases\textsuperscript{81,82} such as metabolic syndrome and type 2 diabetes mellitus which have all been bidirectionally associated with depression.\textsuperscript{5,83,84} At this point we refer to a key topic of this thesis, obesity, as obesity is a key element in metabolic syndrome and is one of the major causes of type 2 diabetes mellitus. Furthermore, as discussed previously, obesity itself has many possible pathways linking it to depression. There is a clear link between dietary intake and obesity. An unhealthy diet is typically associated with a higher energy intake. This together with lack of physical activity will result in weight gain and ultimately obesity.\textsuperscript{85}

**METHODOLOGICAL CONSIDERATIONS**

Some methodological considerations have already been given in the individual chapters. However, some generic considerations will be considered here.

**Limitations**

\textit{Cross-sectional versus longitudinal studies and causality}

Although several of the chapters in this thesis are based on longitudinal studies, three chapters are based on cross-sectional data. Cross-sectional data only captures one moment in time, and therefore has no temporal sequencing of events. Thus it is not possible to draw conclusions about the direction of association or causation. However, other literature suggests that BMI and diet quality are bidirectionally associated with depression. A previous meta-analysis of longitudinal cohort data\textsuperscript{5} concluded that a higher BMI increased the risk of developing depression and conversely also found that depressed persons were more likely to develop obesity, thus suggesting a bidirectional association. However, whether higher BMI increases the risk of depression (or vice versa) or whether there is a shared link, such as a genetic risk factor, remains unknown. A causal relationship could only be proved by intervention studies which are, due to ethical considerations, difficult to perform.

Both chapter 5 and 6, which analyse the associations between diet quality and depression, are cross-sectional. Although arguments can be made for an association in both
directions, supporting longitudinal literature can only be found establishing that poor diet quality increases the risk of developing depression. Only three longitudinal studies have looked at the effect of depression on diet quality and they found no evidence to support the reverse causality hypothesis. Nonetheless, the literature focusing on the relationship between depression and diet quality is mostly cross-sectional, thus there is limited evidence that diet quality is reduced after the onset of depression. One meta-analysis observed that the relationship between diet exposure and depression ceased to exist when studies were corrected for baseline depressive symptoms leading them to conclude that a low quality of diet maybe a co-committal phenomenon of the early stages of depression without genuinely being associated with depression risk. We and another study found that diet quality is not associated with a history of depression. Thus, if depression is co-committal with poor diet quality, this fact does not necessarily persist after recovery. Again, only experimental studies could prove that poor diet quality causes depression, and a shared link, such as BMI, cannot be eliminated.

Underweight and depression

This thesis has mainly focused on the relationship between obesity and depression. Being underweight was only considered as a separate group in chapter 4. There has been some speculation as to whether the relationship between BMI and depression is U-shaped, that is to say whether, in addition to those with overweight or obesity, those with underweight may be at increased risk of depression. One cross-sectional study indeed shows this “U” shaped relationship. However, given that both unintentional weight loss and weight gain are possible symptoms of depression according to the DSM-V, we cannot eliminate the possibility that the depression state itself is the cause of being underweight. Another longitudinal study also showed evidence for a non-linear relationship between BMI and development of depression. However, this was found only for young men and not for women. Our longitudinal study (chapter 4) showed no evidence that persons who are underweight have an increased risk developing MDD. There was also no difference between the thin children and the normal weight children (chapter 3) in their relationship with lifetime MDD (data not shown) and hence these two categories were eventually combined.
Measurement Instruments

Although the analyses involving NESDA data were based on a clinical diagnosis of depression, the HELIUS and AGES cohorts both used instruments that measured depressive symptoms. These instruments (Patient health questionnaire (PHQ-9) & Geriatric depression scale (GDS)) have cut-off points that have previously been validated for detecting depressive disorders,\textsuperscript{90,91} this is nevertheless the same as a clinical diagnosis. Furthermore, many of the symptoms referred to in the questionnaires can also arise from other conditions, such as loss of memory due to dementia or lack of energy due to a somatic illness, thereby potentially coincidently categorizing a person suffering from somatic problems as depressed. Thus, as mention in the relevant chapters, the ethnic differences are in relations to a set of symptoms instead of a disease, and, in the case of the AGES study, there is no association between childhood overweight/obesity and depressive symptoms in late-life but not necessarily no relationship between childhood overweight/obesity and MDD. Adjustment for confounders, such as age and chronic diseases may partially correct for the coincidental effect of overlapping symptoms between depression and old age or other diseases. Finally, most instruments that measure depression severity cannot be used to distinguish between symptom profiles such as atypical depression or neurovegetative symptoms. Given the heterogeneity between people classified as “depressed”, knowing individual symptom profiles is important in determining the complex relationships between BMI, dietary intake and depression.

Measuring dietary intake is notoriously difficult to achieve with any accuracy. A correlation of 0.5-0.7 with objective dietary intake measures is generally considered moderate by most food frequency questionnaires (FFQ).\textsuperscript{92} Typical problems are over and underestimation of actual food consumption, poor recall and the omission of frequently eaten items from the FFQ. Furthermore, reporting accuracy in the FFQ is possibly associated with disorder severity as depression can influence cognitive function.\textsuperscript{93} Underestimation of actual food consumption is more common in those who have higher BMI’s which would lead to a bias in our results, although assuming the underestimation is consistent across all reported food items, correction for total energy intake will partially correct for this bias. We also removed those with extreme energy intakes, and added
other self-report frequently consumed food items which partially resolved some of these issues.

Population sizes

Although the sample sizes of the cohorts used in this thesis were generally good, the number of participants with overweight/obesity in the AGES study was low. Despite data on 889 participants only 101 had elevated GDS scores and 36 had lifetime MDD, leaving our analyses underpowered. Despite this we still found a significant association between overweight/obesity at age 8 and lifetime MDD assessed during late-life. This suggests that there is a relationship between these two variables although the effect sizes found must be taken with caution, and further research needs to confirm our findings.

Strengths

There are several positive aspects to the cohorts used in this thesis. Firstly, with the exception of the AGES study, the sample sizes were large (NESDA baseline N=2,981, 9-year follow-up N=2069, HELIUS N=22,165). Secondly, we had data on a large number of European ethnic minorities with in the HELIUS study. The AGES cohort availed data from a long period, measured anthropometric data from childhood as well as data from late-life.

Additionally, the NESDA cohort included participants from a wide variety of background, thereby encompassing a wide range of depression symptoms, subjects with either depression and/or anxiety and a variety of clinical trajectories. Thirdly, in all of the studies the anthropometric variables were measured by trained assistants and for most studies waist circumference measurements were available in addition to BMI, the latter being a more crude measure of obesity.

Finally, data was available on physical activity, an important confounder, for all three cohorts.
CLINICAL IMPLICATIONS

This thesis shows that higher BMI and obesity increase the risk of developing depression. From a practical point of view, health professionals should be aware that obesity is a risk factor for the development of depression. Additionally, the fact that even being overweight as a child may not only impact physiological health, but may also have long-term consequences for adult mental health, although not geriatric, is important. Furthermore, knowing that the relationship between obesity and depressed mood is not universal among ethnic groups may help target prevention strategies with the knowledge that for some ethnic groups, programs aimed at targeting obesity may result in an improvement in both somatic and mental health and whilst in other groups the improvement in physical health would be the main focus.

Extrapolating the notion that obesity is a risk factor for depression might lead us to conclude that weight loss among obese persons could potentially reduce their risk of developing depression or improve depressive symptoms. High quality randomized controlled trials investigating the effect of weight loss on depression are scarce. One study by Naparstek et al. randomized 136 obese participants to either an internet based weight loss (IBWL) program plus a community initiative, or to community initiative alone for 3 months. They found that participants who received IBWL experienced significantly greater weight loss along with a significant improvement in depressive symptoms compared to the control group. However, as the IBWL consisted of strategies to reduce calorie intake and increase physical activity it is unclear whether it was the weight loss resulting from the reduced calorie intake that was responsible for the reduction in depressive symptoms or the increase in physical activity. This is important as physical activity itself is known to reduce depressive symptoms irrespective of weight loss. Another study by Brinkworth et al. administered either a very low carbohydrate high fat diet or a high carbohydrate low fat diet to 115 obese participants with type 2 diabetes mellitus. Both diets were energy restrictive and isocaloric. After a year, weight loss was achieved in both groups along with significant improvement in depressive symptoms (Beck Depression Inventory). However, as with the previous mentioned trial, physical activity was included as part of the intervention, thus it is not possible to disentangle the
effects of the weight loss and increase in exercise from each other. Finally, a meta-analysis of intentional weight loss RCT studies and their effect on depressive symptoms concluded that, on average, obese individuals in weight loss trials experience a reduction in depressive symptoms.\textsuperscript{97} This study found that trials using exercise treatments alone had the greatest effect size, whilst trials that included lifestyle modifications, where exercise and dietary instruction were combined with behavioural therapy, had a moderate effect on depression. Post-hoc analysis, however showed that reduction in weight was not significantly related to changes in symptoms of depression. This would imply that it is not the weight loss that has a positive impact on depressive symptoms. An alternative source of evidence can be found among clinical trials investigating the effect of weight loss after bariatric surgery. A trial by Yubero-Serrano et al. showed that many patients experience correlated improvements in weight loss and depressive symptoms during the 6 months following surgery.\textsuperscript{98} However, the generalisability of these results are limited as patients who undergo bariatric surgery have extreme obesity with BMI’s >40kg/m\textsuperscript{2}. Furthermore, it is not known whether the improvement in depressive symptoms are due to the actual fat loss or the improvement in body satisfaction, reduction in stigma or the enforced healthier eating habits. In summary, the evidence that weight loss may improve depressive symptoms is inconclusive. Furthermore, taking a realistic approach, weight loss is proven to be a challenging health issue and the subsequent weight maintenance is even more difficult to achieve.

The comorbidity between obesity and depression can have negative consequences with regard to treatment of each condition. On the one hand, weight loss programs for obese persons may be hampered by reduced adherence to the required lifestyle changes because of the concurrent depressive symptoms.\textsuperscript{99} On the other hand, treatment of depressed patients who are comorbid obese may require different treatment to their non-obese counterparts. The obesity related biological dysregulations (e.g. increased inflammation) prevalent in obese depressed patients have been associated with a more chronic course of depression and a poorer response to antidepressants.\textsuperscript{42} It has been proposed that part of the heterogeneity of depression may be due to the differing underlying biological dysregulations. Metabolic dysregulation including obesity and inflammation appear to be more specific to an atypical pattern of depression with increased appetite, weight gain,
and leaden paralysis, as determined by latent class analysis.\textsuperscript{54,55} On the other hand, hypercortisolemia is more specific to melancholic class of depression showing the highest proportions of melancholic symptoms (decreased appetite, weight loss, psychomotor change, lack of responsiveness, diurnal variation, and early morning awakening).\textsuperscript{40,55} This is relevant as treatment strategies for the different depressive subtypes may differ. For example, although it has been found that anti-inflammatory treatment is effective in reducing depressive symptoms,\textsuperscript{100} one study has shown that this is more effective in treatment resistant patients with high baseline CRP levels and higher BMIs, thus atypical or metabolic depressive subtypes.\textsuperscript{101}

The fact that persons suffering from MDD are more likely to gain weight over a 6-year period compared to their healthy counterparts is of clinical importance as weight gain is a risk factor for physiological complications such as diabetes and cardiovascular disease and is thus something that should be monitored.\textsuperscript{102,103} Moreover, weight gain may lead to poor self-image and increased inflammation, which could further exacerbate depressed status.\textsuperscript{104} Our finding, which is supported by other studies,\textsuperscript{105} that antidepressant use is not only cause of weight gain, is also of clinical relevance. This knowledge should help physicians give better treatment advice, as fear of weight gain in particular is a major reason for drug treatment non-compliance in depressed patients\textsuperscript{106} and may contribute to a hesitancy to start with antidepressant treatment.\textsuperscript{107} Finally, monitoring weight loss in patients diagnosed with MDD is also important as this can lead to osteoporosis, sarcopenia, and frailty.\textsuperscript{108–110}

Our findings would suggest that a healthy diet such as the Mediterranean diet, high in whole grains, vegetables and fruit, may be a way of reducing depressive symptoms and would concurrently help to reduce obesity, however conformational experimental evidence is required before a healthy diet as treatment can be advocated. One meta-analysis of prospective observational studies summarizing the influence of diet on depression suggested that although dietary changes appear to prevent depressive symptoms, the overall impact of diet is small.\textsuperscript{34} The fact that dietary changes are difficult to make or maintain makes this a more challenging approach to the reduction depressive symptoms.\textsuperscript{111} More positive evidence demonstrating that dietary changes could contribute
to the treatment of depression can be found in two clinical trials. One clinical trial among 152 depressed participants found that a Mediterranean diet supplemented with fish oil resulted in a significantly greater improvement in depressive symptoms over a 6 month period compared to a group that only participated in social interaction.\textsuperscript{112} Another smaller intervention study (n=67) gave either dietary intervention or social support to moderately or severely depressed participants.\textsuperscript{113} The dietary intervention comprised personalised dietary advice and nutritional counseling support, including motivational interviewing, goal setting and mindful eating, from a clinical dietician in order to support optimal adherence to the recommended Mediterranean-like diet. The dietary intervention groups showed a significantly greater improvement in depressive symptoms, independent of any weight change, compared to the group receiving social support over the 12 week period. In conclusion, although these small studies indicate that dietary improvement may provide an efficacious and accessible treatment strategy for the management of depression, more evidence from high-quality studies is needed.

RECOMMENDATIONS FOR FUTURE RESEARCH

This thesis adds and broadens epidemiological evidence confirming the relationship between both BMI/obesity and dietary intake with depression as well as expanding upon clinical aspects of these relationships. However, this thesis also raises some points which warrant further investigation.

Firstly, although we found that the relationship between obesity and depressed mood is not consistent across ethnic groups, we could only speculate as to why these differences exist. Future studies should explore whether differential social-cultural based normative values or underlying pathophysiology across ethnic groups explain why obesity and depression are strongly related in some but not all ethnic groups.

Secondly, our research implies that childhood weight is a possible risk factor for subsequent adult mental health, although these results must be interpreted with caution as in our population the prevalence of overweight and obesity and reported MDD was low. There is currently too little evidence to determine whether it is childhood
overweight/obesity that is possibly increasing the risk of subsequent MDD or other factors that may precipitate childhood overweight/obesity, such as childhood trauma or an unhealthy diet or consequential factors, such as bullying. Thus, given that childhood obesity is currently a large public health problem, studies examining measured childhood overweight/obesity, childhood events, diet, bullying in conjunction with lifetime MDD in populations where childhood obesity is more prevalent are warranted. Furthermore, it would be useful if such studies could also incorporate biological measurements such as cortisol levels and inflammatory markers as well as psychological questionnaires to help elucidate the mechanism behind the development of depression.

Thirdly, our results suggest that being obese is a risk factor for the development of depression, however there is a lack of intervention studies that investigate the independent effects of weight loss through caloric restriction without additional physical activity as well. The ethics of eliminating physical activity advice from any weight loss programme is debatable, however alternative options, such as comparing changes in depressive symptoms between groups that only do physical activity compared to caloric restriction and physical activity is feasible.

Fourthly, our studies into diet quality and depression were performed on cross-sectional data. Although there are plenty of longitudinal studies establishing the link between poor diet quality and the development of depression, few studies examine whether the quality of diet is reduced during a longitudinal trajectory of depressive episode development and whether such a relationship discontinues during episode recovery.

Finally, there is a lack of large clinical trials investigating whether a healthy diet can reduce the risk of developing depression or improve depressive symptoms in persons already suffering from MDD. The current clinical evidence is limited by small numbers of participants, or the fact that the dietary intervention was given in combination with dietary supplements, making it impossible to disentangle the effects of the two. The results of the MooDFOOD depression prevention study will help answering the question as to whether a higher diet quality can reduce the risk of developing depression. This trial was set up in 2015 and aimed to examine the feasibility and effectiveness of two different
nutritional strategies to prevent a new episode of MDD in high-risk overweight persons with sub-syndromal symptoms of depression. Using a two-by-two factorial design this study recruited over 1000 participants equally divided over four groups to receive either a 1) food-related behaviour activation therapy (FBA) (aimed at improving diet quality and reducing poor eating habits) together with a vitamin and mineral supplements, 2) vitamin and mineral supplementation and no FBA, 3) placebo pills and FBA, 4) placebo pills and no FBA. Baseline and follow-up measurements (3 months, 6 months & 12 months) measured among other things depressive symptoms and the development of MDD. The results of this trial will be published soon.

CONCLUSION

Obesity (and being overweight in childhood) and a higher BMI or waist circumference are risk factors for the development of, although not the persistence of, clinical major depressive disorder. Additionally, higher BMI/obesity during childhood is not related to elevated depressive symptoms measured during late-life. The relationship between depression and BMI is not necessarily consistent for all groups of people, for instance over ethnic groups, as found in our analysis in a large multi-ethnic cohort. Furthermore, being clinically depressed is also associated with subsequent weight loss or weight gain over a 2-year period, regardless of antidepressant use. Over a 6-year period, persons with a current depressive disorder are more likely to gain weight than persons who have no current depressive disorder.

The relationship between obesity and depression is complex and there are many possible underlying mechanisms. Most likely a combination of factors plays a role and given the heterogenetic nature of depression, it is also feasible that the mechanisms vary according to the unique combination of symptoms.

Having a current clinical diagnosis of depression and/or anxiety disorder is associated with a poorer quality of diet. The association is mostly driven by severity of the disorder, the more severe the symptoms, the poorer the quality of diet. Although non-refined grains and, to some extent vegetables, appear to be particularly important in the
relationship between diet and depression/anxiety disorders, it is the combined effect of the whole diet that has the largest association with depression and anxiety. Due to the cross-sectional nature of our dietary studies we cannot conclude whether it is a poorer diet that leads to the development of depression or whether suffering from depression prohibits healthy eating, thus resulting in a poorer diet quality. Most likely the relationship is bidirectional.

The growing prevalence of obesity among developing and developed countries will only increase the problem of physical and mental health in society. Trends in food consumption where fast, readily consumable, unhealthy food is more widely available will exacerbate this problem. Improvement of diet quality and prevention of obesity are two important public health targets which will not only help reduce the number of chronic diseases but could also lead to an improvement in mental health.
REFERENCES


48. Howren, M. B., Lamkin, D. M. & Suls, J. Associations of depression with C-reactive protein, IL-1,


81. Jannasch, F., Kröger, J. & Schulze, M. B. Dietary Patterns and Type 2 Diabetes: A Systematic


98. Preiss, K. *et al.* Psychosocial Predictors of Change in Depressive Symptoms Following Gastric


