Chapter 1

GENERAL INTRODUCTION
Obesity and depression are major public health problems, posing enormous challenges for the decades to come. Although the direction of the association between obesity and depression remains unclear, their co-occurrence in an individual may have negative consequences on work and health. The aims of this thesis were to examine the association between obesity and depression, and to examine their separate and combined effects on long-term sickness absence, work performance, health-related quality of life and health care utilization and costs. This chapter presents the key concepts of the thesis, and provides the rationale for studying obesity and depression together in relation to work and health outcomes. It also describes the aims, introduces the research questions within a conceptual framework, and provides an outline of this thesis.

Definition of obesity
The World Health Organization (WHO) defines obesity as an abnormal or excessive fat accumulation in adipose tissue, to the extent that health may be impaired (1). Obesity is recognized as a disease according to the International Classification of Diseases 10th Revision (ICD-10) code E66 (2). The pathology of obesity involves a regional distribution of adipose tissue, often accompanied by profound changes in physiological function (3). An accumulation of adipose tissue around and inside the abdominal organs, called intra-abdominal obesity, is associated with a higher risk of morbidity and mortality (4,5).

The most common method used to assess obesity is the body mass index (BMI), which is calculated as [(weight in kg)/(height in m)^2]. BMI measurement is a simple, rapid, and inexpensive method that can be applied generally to adults in clinical practice and research. BMI is significantly correlated with total body fat as well as morbidity and mortality. According to the WHO, a state of having a BMI of ≥ 30 kg/m^2 is defined as obesity, while a BMI of > 25 kg/m^2 is overweight. A BMI of 18.5–25 kg/m^2 is normal, and by definition a BMI of > 25 kg/m2 is abnormal (1). Waist circumference (WC) is an alternative measure for obesity, relating both to total fatness and specifically to intra-abdominal adiposity (6). Having a WC of ≥102 cm for men and ≥88 cm for women is defined as abdominal obesity (1, 7). Although the most common causes of obesity are overeating and physical inactivity, there is no single cause that can explain all cases of obesity. There is general agreement that the etiology of obesity is multifactorial and involves genetics, metabolism, environment, behavior and culture (8-11).
Global and national burden of overweight and obesity

Obesity is currently a global health threat, and its prevalence has reached epidemic levels (13). Since the 1980s the number of overweight and obese people in the world has more than doubled, increasing from about 850 million people to over 2 billion (12). Obesity burden projections indicate that by 2030 up to 57.8% of the world’s adult population (3.3 billion people) could be either overweight or obese (13). In high-income countries, the prevalence of obesity ranges from 10% to 30%, highest in the WHO regions of the Americas (62% for overweight, and 26% for obesity) and lowest in the WHO region for Southeast Asia (14% overweight in both sexes and 3% for obesity) (14). About 3.4 million adults die each year as a result of being overweight or obese, and an estimated 35.8 million (2.3%) of global disability adjusted life years (DALYs) are caused by overweight or obesity (1,12). The risk of coronary heart disease, ischemic stroke and type 2 diabetes grows steadily with increasing body weight. The WHO estimates that globally 44% of the diabetes burden, 23% of the ischemic heart disease burden, and 7% to 41% of certain cancer (e.g. breast, colon and prostate) burdens are attributable to overweight and obesity. Currently, 52% of the European adult population is considered overweight or obese (1). In 2012, Statistics Netherlands reported that 48% of the Dutch adult population was overweight, including 12% obese, which costs the nation around 887 million Euro per year (15,16).

Definition of major depression

Major depression, also called major depressive disorder (MDD) or clinical depression (both further referred to as depression) is a serious medical condition that affects one’s thoughts, feelings, behavior, mood and physical health. Most people occasionally feel blue or sad, but these feelings usually go away within a couple of days. When a person has a depressive disorder, it interferes with daily life and normal functioning and affects a person’s loved ones (17).

Depression is widely diagnosed using the criteria from the Diagnostic and Statistical Manual of Mental Disorders version IV (DSM-IV) of the American Psychiatric Association (17). According to these criteria, persons who suffer from depression must have at least one of the core depressive symptoms (i.e., either depressed mood or diminished interest or pleasure in daily activities) and a total of 5 or more depressive
symptoms, such as significantly diminished interest or pleasure in all, or almost all activities; significant weight gain, or weight loss when not dieting, or decrease or increase in appetite; body agitation or retardation; tiredness or loss of energy; trouble falling sleep or sleeping too much; feelings of worthlessness or excessive guilt, recurrent thoughts of death, recurrent suicidal ideation or a suicide attempt. These symptoms need to be present most of the day, nearly every day, for at least two weeks and must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning (17).

Depression is in its manifestation and etiology a heterogeneous disease (18). The depressive episode may occur only once in a person's lifetime, better known as major depressive disorder-single episode (MDD-S) or it may recur throughout a person's life, better known as major depressive disorder-recurrent episode (MDD-R) (17). This heterogeneous clinical feature of depression makes the disease more challenging to understand (19). The general scientific understanding is that depression does not have a single cause but arises from multiple factors. A person’s life experience, genetic inheritance, age, sex, hormone changes, substance use and other illnesses can all play significant roles in the development of depression (20-32). In spite of this heterogeneity, however, research on depression is most often monodisciplinary. Research that crosses boundaries between disciplines (e.g. Psychiatry and Bariatrics) is limited, a fact which precludes an integrated understanding of depression.

**Global and national burden of depression**

The Global Burden of Disease analyses of the WHO showed that depression is worldwide the third leading cause of disability at all ages and takes the first place in middle- and high-income countries. By 2030, depression is even expected to rank first in disease burden in the high-income countries (18). The average lifetime and 12-month prevalences of MDD are 14.6% and 5.5% in high-income and 11.1% and 5.9% in low- to middle-income countries (33). In the general US population, the lifetime incidence of MDD is 16% (34). Antidepressant medication (ADM) is currently one of the most commonly prescribed classes of medication in outpatient medical practices in the US (35). In the Netherlands, the average lifetime and 12-month prevalences of MDD are 17.9% and 5%, respectively. The Netherlands ranked third out of the ten high-income countries included in the survey:
Obesity and depression

As indicated earlier, both obesity and depression are widespread problems with major public health implications. Although research is less advanced in understanding the relationship between obesity and depression, recent studies suggest that the two may be bi-directionally linked (36,37). Data from the National Health and Nutrition Examination Surveys, 2005–2010 showed that 43% of US adults with depression were obese, and adults with depression were more likely to be obese than adults without depression (38). Body image dissatisfaction, weight-related stigma and discrimination, and emotional eating are the proposed underlying mechanisms linking obesity and depression (39).

When a person is under sustained stress or depression, he/she may use food as a primary coping strategy for emotion regulation, which may in turn lead to obesity (40-42). Grenon et al showed that one third of obese women with binge eating problems had a current depressive disorder and two thirds had a lifetime depressive disorder (40). The Hypothalamic–Pituitary–Adrenal (HPA) Axis is another possible mechanism linking depression and obesity. The HPA axis is a part of the nervous system which excretes a variety of hormones and keeps body chemicals balanced. It releases cortisol to counteract the effects of distress or depression (43,44). The resulting high blood level of cortisol may decrease insulin sensitivity and raise fat deposits around the waistline. Cortisol is also involved in promoting differentiation and proliferation of human adipocytes, which have been shown to be positively associated with an increased risk of BMI and abdominal obesity (43-45). However, despite efforts to explore the complicated psychological and physiological links between obesity and depression, the direction of the association is as yet unclear. Prospective studies may help to disentangle this direction of association.

Why is it important to study obesity and depression together?

Obesity and depression often coexist, and both can affect an individual’s health and productivity. We examine in this thesis the combined or joint effects of obesity and depression on work and health outcomes for several reasons. First, obesity and
depression are prevalent health problems nationally and globally (1,13,34,46). Second, both problems are major risk factors for common chronic diseases including diabetes II, cardiovascular diseases, chronic kidney disease and cancer, and they are also associated with disability and premature death (13,34,47). Third, obesity and depression often co-occur and are inter-related (36,37). Growing evidence indicates that inflammation may play a significant role in the potential relationship between these two conditions (47-50). Fourth, studies have found a modest overlap in the genetic risk factors that increase liability to both obesity and depression (51-53). It seems that the two may have a common etiology or triggering mechanisms, which make them valuable to examine. Fifth, treatment for obesity has been found to actually exacerbate depression, and vice versa. For example, obesity treatments such as dieting may worsen mood in general, and particularly if there is repeated failure. This may lead to depression and suicidality (54). Conversely, some pharmacological treatments for depression have obesogenic effects (weight gain), e.g. Fluoxetine, Sertraline, Citalopram (55).

Despite all these facts, obesity and depression have mostly been treated as two independent conditions and research fields, and their potential synergistic effect on adverse work and health outcomes has not been considered. This hampers an integrated understanding of obesity and depression, and until now may even have contributed to the low success rates in prevention and management of obesity and depression. Some advanced efforts have been made to identify important risk factors for obesity and depression, but in the past three decades no national success stories have been reported, especially for obesity (12).

**How to study obesity and depression together?**

The relationship between obesity and depression is complex, and neither one solely surpasses the other in its effect on work and health outcomes. Therefore, the two conditions should best be assessed simultaneously to explore the effects of their interaction on outcomes of work and health. In terms of their interaction effects on the risk of adverse outcomes, obesity and depression may augment or reduce the effect of one another. If obesity and depression exacerbate a shared pathway, we expect to observe substantially elevated risks in people with both exposures.
Two exposures of interest on a certain outcome can be assessed by statistical interaction on the additive scale using measures such as the Synergy Index (SI), the relative excess risk due to interaction (RERI) and the attributable proportion (AP) (56,57). Statistical interaction on the additive scale is relevant to disease prevention and workplace health promotion programs for vulnerable workers. It indicates whether the joint effect of two risk factors on the outcome is larger or smaller than the sum of the separate effects. If the joint effect of obesity and depression is larger than the sum of individual effects on a certain outcome, this will indicate whether intervening in either obesity or depression would be more beneficial than intervening in both conditions; this knowledge may in turn have public health and economic implications. Especially in resource-limited settings, it would help to identify the vulnerable subgroup of individuals for whom intervening on a certain exposure would have the largest effect. Even in settings with unlimited resources a particular intervention that is beneficial for some individuals could be harmful for others. Hence, the effects of potential interactions between obesity and depression on work and health outcomes warrant detailed investigation in the working and general population.

**Effects of obesity and depression on work**

Given the deleterious effects of obesity and depression on health, they are also likely to have negative consequences for work. A healthy and productive workforce is critical for economic success and general well-being. Health-related productivity loss arises from two sources: absenteeism and presenteeism (58-60). Absenteeism refers to an employee’s time away from work due to health conditions, also known as sickness absence (58). Presenteeism refers to being present at work, but impaired in some aspects of job performance by a health problem, implying hidden costs for employers (59). Absenteeism and presenteeism are increasing problems in aging workforces and have enormous cost implications for individuals, companies and society as a whole (61,62). The rapid worldwide rise of obesity and its frequent co-occurrence with depression have prompted recent evaluations of the extent of their burden on work productivity.

**Long-term sickness absence**

Long-term sickness absence (LTSA) is an important negative work outcome and has in recent years received considerable scientific and political attention in many European
countries. It is also a public health risk marker for morbidity and mortality, and an economic risk marker for disability pensioning (63,64). In the Netherlands, sickness absence, particularly of more than 2 consecutive weeks, costs almost €20 billion annually (65).

Overweight, obesity and psychological distress can contribute to LTSA. Increased medical problems such as musculoskeletal disorders, osteoarthritis, rheumatoid arthritis, carpal tunnel syndrome and mobility restrictions associated with obesity can have a direct impact on psychological well-being, leading to clinically significant distress or depression (41,54). Attempts to control weight are also challenging and distressing, and repeated failure of attempts to lose weight may lead to clinically significant distress (54), which may in turn result in more excess weight. Such psychological difficulties combined with being overweight can increase the risk of LTSA among employees. However, most studies have considered overweight and distress separately without taking into account the potential synergy in their impact on LTSA.

Work performance impairment

Work performance impairment (WPI) is another important work outcome. WPI refers to the reduction of performance at work because of physical health or emotional problems (66). It is an increasing problem in aging workforces and has enormous societal implications because a large proportion of individuals with health problems remain at work. Earlier cross-sectional studies showed that depression is associated with high WPI (67,68), and accounts for the majority of economic costs of productivity loss due to presenteeism. A review by Schultz et al showed that the percentage of these total costs ranged from 27% to 81% (59). More severe depressive symptoms were associated with more work limitations, while poor clinical improvement was related to a reduction in work productivity (69). Higher body weight and excessive visceral fat were similarly associated with productivity loss (70-72).

Obesity and depression can impair work performance and reinforce each other. Obese persons have a higher risk of developing depression over time and vice versa (36). Obesity and depression are also associated with risks of other adverse health conditions (13,34). Therefore, it would seem that employees suffering simultaneously from obesity
and depression are at greater risk of high WPI than those with only obesity or only depression. However, evidence regarding this combined effect is lacking.

**Effects of obesity and depression on health-related quality of life**

Health-related quality of life (HR-QoL) refers to an individual's subjective perception of both positive and negative aspects of life as influenced by his health status (73). It indicates the person’s sense of well-being and ability to perform social roles including the work-role. HR-QoL has gained increasing interest as an outcome measure in clinical medicine and public health settings. As HR-QoL measures elucidate patients’ overall sense of well-being and perception of their own health status, they can be considered as adjuvant to healthcare services and outcome assessment for many chronic conditions including obesity and depression (74). They may also help to identify specific and general health needs and guide public health policy.

Previous studies have shown that obesity and depression have a negative impact on HR-QoL (75,76). As obesity and depression also have an earlier age of onset than other chronic conditions, their cumulative long-term effect on HR-QoL could be substantial. Moreover, the two conditions affect each other and can lead to poorer HR-QoL. This suggests that persons with both obesity and depression may have poorer HR-QoL than persons with only one of the conditions. However, to date, little is known about the potential combined effects of the two on poor HR-QoL, especially in the general population. Such knowledge would be a valuable contribution to that currently offered by traditional medical and clinical measures.

**Effects of obesity and depression on health care utilization and costs**

The obesity epidemic is responsible for over one-fourth of the spiraling growth of US healthcare costs in the past two decades (77). By 2030, obesity is projected to affect 50% of the US population, and account for 16% to 18% of total healthcare expenditures (78). Having a BMI of greater than 30 and 40 has been associated respectively with 50% and 100% increases in health care costs per capita (79,80). Obesity is also consistently associated with high health care utilization (HCU), such as use of primary and specialized care, and hospitalization (79-81).
Higher incidences of depressive and anxiety disorders and their comorbid somatic conditions (9, 82-84) can lead to increased service use and costs in the health care system. Earlier studies showed that one in three adult primary care patients has a full or subclinical depressive disorder (85, 86). Depression is also associated with a 50 to 75% increase in health care costs per capita (87).

Both obesity and depression can increase HCU and impose large and increasing health care costs on society. Both conditions are tied to health risks like diabetes and heart diseases, and being obese may increase patients' risk of depression and vice versa (36). This suggests that one condition exacerbates the other, thereby increasing HCU and associated costs of care. Thus, persons suffering from both obesity and depression are more likely to consume more health care resources compared to those suffering from either condition alone. It is, therefore, important to examine over time the effect of these two factors on high HCU and costs and to estimate to what extent their combined effect differs from their separate effects. Such research will help to identify cost drivers and provide some explanation for the observable increases in total health care costs in the Dutch population.

**Aim of the thesis and research questions**

The aims of this thesis were to examine the direction of the association between obesity and depression, and to examine their separate and combined effects on long-term sickness absence, work performance impairment, health-related quality of life, and health care utilization and costs. The conceptual model of the thesis is shown in Figure 1. Six main research questions, listed below, were formulated based on the overall aim of the thesis.
Research question 1:  
What is the direction of the association between obesity and depression? Does single or recurrent episode matter? (Chapter 2)

Research question 2:  
Is there a joint association between overweight and distress with long-term sickness absence? If yes, is this joint association greater than the sum of the separate associations of overweight and distress with long-term sickness absence? (Chapter 3)

Research question 3:  
Is obesity associated with work functioning? And what role do working-time arrangements play in this association? (Chapter 4)

Research question 4:  
Are obesity and depression longitudinally associated with an increased risk of high work performance impairment? Is the joint association of obesity and depression greater than the sum of the separate associations of obesity and depression with high work performance impairment? (Chapter 5)

Research question 5:  
Are obesity and depression or anxiety associated with poorer health-related quality of life in the general population compared to obesity alone and depression or anxiety alone? (Chapter 6)
Research question 6:

Does obesity along with depression or anxiety lead to higher health care use and costs compared to obesity alone and depression or anxiety alone? (Chapter 7)
Data sources and measures
To answer the research questions we used several data sources with cross-sectional and longitudinal design across different population groups. Table 1 provides a brief overview of the data sources, design, core variables and measures by chapter.

Table 1: Overview of the data sources, design, core variables and measures in this thesis

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<thead>
<tr>
<th>Data source</th>
<th>Study design</th>
<th>Core variables</th>
<th>Measure</th>
<th>Role in analysis</th>
<th>Chapters</th>
<th>Way of measurement</th>
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<td>Independent and dependent</td>
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Note: PREVEND: Prevention of renal and vascular end stage diseases; BMI: Body Mass Index; CIDI: Composite International Diagnostic Interview; LTSA: long-term sickness absence; 4DSQ: Four-dimensional Symptom Questionnaire; WF: Work functioning; WRFQ: work-role functioning questionnaire; NESDA: Netherlands study of depression and anxiety; WPI: work performance impairment; HCU: health care utilization; WC: Waist circumference; Tic-P: Questionnaire for costs associated with illness; HR-QoL: Health-related quality of life; MINI: Mini-International Neuropsychiatric Interview; RAND-36: RAND 36-item medical outcomes survey.
Outline of the thesis
This thesis consists of eight chapters, including this general introduction. In Chapter 2 we examine the prospective association between obesity and depression and whether depression subtypes have different effects on obesity or vice versa. In Chapter 3 we assess the separate and joint associations of overweight and distress with long-term sickness absence among Dutch employees. In Chapter 4 we examine the association of overweight and obesity with work functioning, and whether these associations differ between workers with different working-time arrangements (i.e. day workers, on call workers and shift workers). In Chapter 5 we investigate the longitudinal joint effect of obesity and depression at a given point in time on high work performance impairment during a 6-year follow-up period in the Netherlands study of depression and anxiety. We also examine whether the joint effect of obesity and depression on high work performance impairment is greater than the sum of their separate effects. In Chapter 6 we examine the combined effects of obesity and depression/anxiety on health-related quality of life in a large population-based cohort study, the LifeLines cohort study. In Chapter 7 we examine the separate and joint longitudinal associations of obesity and depression/anxiety with high health care utilization and costs in the Netherlands study of depression and anxiety. In Chapter 8 we provide a general discussion of the research findings in a broader context, give extensive treatment of related methodological issues, and explore directions for future research and implications for clinical practice.
REFERENCES


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