DEPRESSION AND ANXIETY IN TYPE 2 DIABETES: ASSOCIATIONS WITH DIABETES ONSET, CLINICAL MANAGEMENT, AND LONG-TERM MORTALITY

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ABSTRACT

Type 2 diabetes is a highly prevalent disease which could affect roughly 552 million people globally by the year 2030. In addition to a range of medical complications, individuals with diabetes experience higher rates of mental illness (e.g., depression and anxiety) than the general population. A growing body of evidence suggests that depression may exert important influences at key stages of the diabetes experience, including: diabetes onset, diabetes management, and mortality. A smaller body of research has explored the influence of anxiety on diabetes outcomes, and anxiety is demonstrated to elicit similar effects on the dysregulation of endocrinological or behavioural process as depression. This is of concern given that depression and anxiety co-occur in the majority of primary care cases, and individuals experiencing both disorders tend to have poorer prognoses than either alone. This thesis sought to study the independent and concurrent contributions of depression and anxiety to key diabetes outcomes in a population-based sample of Norwegian adults, through a series of four studies. The first study uses meta-analysis to demonstrate that both depression and anxiety are associated with a moderate increased risk of diabetes onset, and that these effects may only be significant in men. The second study illustrates that the fraction of incident diabetes cases attributable to metabolic and behavioural factors at the population level increases in the presence of depression and anxiety, especially in men. The third study demonstrates that depression and anxiety are differentially associated with some diabetes management outcomes (i.e., glycemic control, c-reactive protein levels, and diet adherence), with variations by patient sex. And the final study provides evidence that long-term mortality risk is lowest in diabetic individuals experiencing anxiety, higher in those with concurrent depression-anxiety, and highest for depression, with variation by sex. Overall, this body of work suggests that both depression and anxiety may result in poorer diabetes outcomes in men across all key stages, while symptoms of anxiety may provide protection against diabetes onset and risk of mortality in women with Type 2 diabetes. Future research should aim to differentiate and control for co-occurring depression and anxiety when examining diabetes outcomes, and report sex-specific estimates as a standard approach.

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INTRODUCTION

Type 2 diabetes is one of the leading public health concerns of the 21st century [1], with a worldwide prevalence of over 8.5% [2]. The current global estimate of approximately 415 million people is projected to increase by two thirds to 552 million by the year 2030 [1]. This equates to a 1 in 11 chance of developing diabetes over an individual's lifetime, with one death occurring every six seconds from this condition [3]. Despite these high rates, as many as one third of individuals with diabetes remain undiagnosed [4]. Diabetes is also a costly condition, with worldwide current spending exceeding $670 billion USD, constituting roughly 12% of global health expenditure [3]. These costs are projected to increase by 20% to over $800 billion USD by 2040 [3]. The recent rapid increases in global diabetes rates are primarily attributed to the rise in high calorie diets and low physical activity associated with the spread of Western lifestyles, coupled with the simultaneous rise in the prevalence of overweight and obesity across developed and developing countries [5]. The causes of diabetes are, however, complex and involve a wide range of well-established risk factors, including obesity, smoking, genetics, physical inactivity, and dietary behaviours [6].

Type 2 diabetes is the predominant form of a group of metabolic disorders that are collectively referred to as *diabetes mellitus*, and alone accounts for 90-95% of all diabetes cases [7]. The main pathophysiological features of Type 2 diabetes are impaired insulin secretion through pancreatic β-cell dysfunction, and decreased sensitivity of target tissues to insulin, known as insulin resistance [8]. The basic consequence of these defects is to disrupt the sensitive interplay between insulin and insulin action, thereby preventing the effective uptake and utilization of glucose by cells

throughout the body [9]. This induces a chronic state of elevated blood sugar, or hyperglycemia, which can be detected through clinical measurements of plasma glucose levels. The thresholds for diagnosing Type 2 diabetes based on indicators of glycemic control are listed in Table 1.1. The chronic presence of excessive glucose in the body that is characteristic of Type 2 diabetes significantly affects the functioning of multiple organ systems, leading to common symptoms such as frequent urination (polyuria), excretion of glucose into the urine (glycosuria), dehydration, excessive thirst, weight loss, blurred vision, and risks of diabetic coma or diabetic shocks due to hyper- or hypoglycemia, respectively [9]. It is also a progressive disease that is associated with a number of more severe and potentially life-threatening complications over time, such as heart disease and strokes, cancers, amputations, kidney failure, retinopathy, and blindness [10–14].

Because of the serious and ongoing nature of these health risks, diabetes is a disease that requires a high degree of professional support, usually through multidisciplinary health care teams that include general physicians, diabetes educators, nurses, endocrinologists, and others. Moreover, it is a disease that requires a high degree of vigilance and self-management on the part of the patient. Patients are encouraged to maintain strict control of blood glucose, blood pressure and cholesterol levels [15] , and are counselled to control their diabetes through a combination of regular exercise, modified diet adherence, routine home monitoring of glucose levels, regular checking of feet for sores or ulcers, medication adherence, and effective stress management [16]. This involves enacting significant lifestyle changes for many individuals, and receiving a diabetes diagnosis and the subsequent burden of coping with the disease can have demonstrable psychological impacts [17]. Like many other chronic conditions (such as cardiovascular disease [18] and cancers [19]), individuals with Type 2 diabetes are markedly more likely to experience psychiatric comorbidities such as depression and anxiety during the course of their lifetimes [17, 20]. The study of comorbid

mental and physical illness has emerged as an important new research area, and accumulating evidence has begun to demonstrate the importance of psychological factors on diabetes outcomes.

Table 1.1: Diagnostic criteria for Type 2 diabetes, major depression and generalized anxiety

Disorder	Diagnostic Criteria
Type 2 Diabetes [3, 21]	*One or more of the following criteria:* • Fasting plasma glucose ≥7.0 mmol/L (126 mg/dl) • 2-hr plasma glucose ≥11.1 mmol/L (200 mg/dl) following a 75g oral glucose load • Hemoglobin A1C assay ≥6.5% • Random plasma glucose ≥11.1 mmol/L (200 mg/dl)
Major Depression [22]	*One or both of the following symptoms within a 2-week period (experienced most of the day, nearly every day):* • Depressed mood (e.g., feels sad, empty or hopeless) • Lost of interest or pleasure in almost all activities, *Plus 4 (or more) of the following symptoms:* • Significant change in weight or appetite • Insomnia or hypersomnia • Psychomotor agitation or retardation • Fatigue or loss of energy • Feelings of worthlessness or guilt • Diminished ability to concentrate or indecisiveness • Recurrent thoughts of death or suicidal ideation
Generalized Anxiety Disorder [22]	*Both of the following:* • Excessive anxiety and worry occurring on the majority of days for at least 6 months • Inability to manage these symptoms *Plus 3 (or more) of the following symptoms occurring for the past 6 months:* • Restlessness, feeling keyed up or on edge • Being easily fatigued • Diminished ability to concentrate • Irritability • Muscle tension • Insomnia or restless sleep

1.1 Depression and anxiety in Type 2 diabetes

Depression and anxiety constitute two of the most common psychiatric disorders globally, and like diabetes, occur at high frequencies in the general population. The worldwide 12-month prevalence of depression is estimated to be 4.4%, equivalent to over 320 million people [23]. The corresponding prevalence of anxiety disorders is 3.6% globally, equivalent to 264 million people [23]. Lifetime prevalences of both disorders are far higher, with rates rising as high as 20.8% for depression and 33.7% for anxiety [24, 25]. Depression is ranked by the World Health Organization as the single largest contributor to global disability, and anxiety disorders are currently ranked 6th, accounting for 7.5% and 3.4% of all years lived with disability in 2015, respectively [26]. Table 1.1. lists the diagnostic criteria for major depression and generalized anxiety disorder, according to the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V).

1.1.1 Depression and Type 2 diabetes

Major depression and Type 2 diabetes are each predicted to be among the five leading causes of morbidity and health loss by 2030 [27]. Type 2 diabetes, depression and anxiety can be independent or interrelated, as illustrated in Figure 1.1. This figure also diagrams the three potential comorbidity types that may occur between Type 2 diabetes and the presence of depression and anxiety: 1) Type 2 diabetes comorbid with depression, 2) Type 2 diabetes comorbid with anxiety, and 3) Type 2 diabetes comorbid with concurrent depression-anxiety. The size of the evidence base varies for each of these comorbidities, and an overview of the current literature relevant to each one is given below.

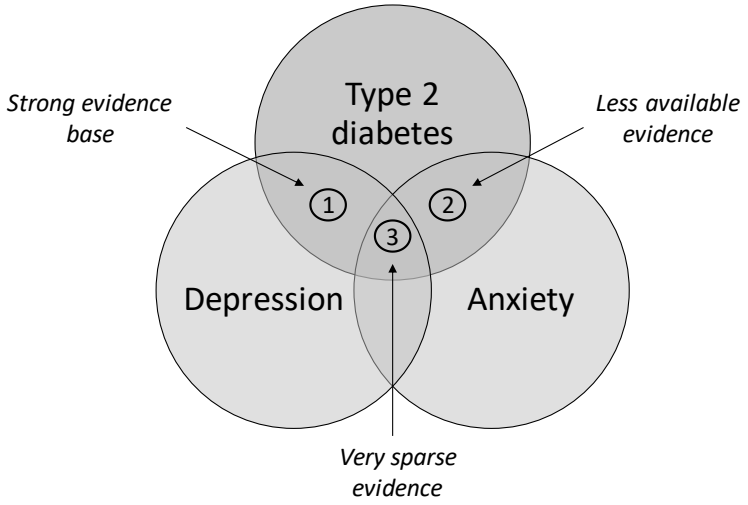


Figure 1.1: Diagram of potential comorbidities between depression, anxiety, and Type 2 diabetes

A long history of observation of the relationship between depression and diabetes has been documented, dating as far back to the British physician Thomas Willis in 1684 [28]. In addition to being the first physician to identify glycosuria as a sign of diabetes [29], Willis suggested the disease often resulted from 'sadness or prolonged sorrow and other depressions and disorders' [28]. A series of experiments conducted throughout the late 19th century demonstrated the appearance of glucose in the urine following exposure to stressful stimuli in both cat and human subjects [30], which was given the term 'emotional glycosuria'. Between 1900 to 1950, many observations were made in the literature regarding the sudden or spontaneous appearance of diabetes associated with traumatic events [31, 32]. In 1935, Menninger published a study of 22 cases of mental disorder associated with diabetes [33], which was followed in 1946 by a paper in *The New England Journal of Medicine* by Gendel and Benjamin, titled "Psychogenic factors in the etiology of diabetes" [30]. In 1948, George Daniels published an article in *Psychosomatic Medicine* detailing the role of emotion in the onset and course of diabetes [34], along with a series of other papers on psychosomatic approaches to diabetes treatment [35, 36]. But it was not until

the 1990s that the topic started to gain significant traction, and research on the emotional causes and consequences of diabetes began in earnest.

Since then, a large number of high-quality epidemiological studies and meta-analyses have demonstrated that diabetic populations experience depression at roughly double the expected rates [20, 37], with estimates ranging from 11% to as high as 47% in some studies [20, 38]. In an attempt to explore potential causal and etiological linkages between depression and diabetes, numerous longitudinal studies have also been performed. These studies reveal the bidirectional nature of this relationship [39, 40], the majority of which report stronger effects of depression predicting diabetes than for the reverse association (e.g., OR=1.60 versus OR=1.15 [40]). A wealth of research now suggests that depression is associated with all stages of the diabetes continuum. For example, insulin resistance and prediabetes are both important precursors to Type 2 diabetes onset. A meta-analysis of 18 studies examining the relationship between depression and insulin resistance found a significant pooled standardized effect size of 0.19 (although this review included cross-sectional studies) [41]. A more recent longitudinal study of depressive symptom clusters and insulin resistance found a highly significant linear relationship between baseline Beck Depression inventory scores and insulin resistance over 6 years (β=0.14) [42]. Although the preceding effects are small in size (but significant), the evidence relating to diabetes onset itself has been much more convincing. Prediabetes is a condition characterised by hyperglycemia that falls just below the threshold for diabetes (i.e., 5.6 to 7.0 mmol/L)[43]; the majority of individuals with prediabetes will progress to diabetes in the absence of intervention, and reported rates of conversion can reach as high as 70% [44]. Depression has been found to more than double an individual's risk of progressing from prediabetes to diabetes over a period of 4.5 years (OR=10.65 versus 4.14) [45], and the joint effect of depression and prediabetes has been demonstrated as having a synergistic

effect on diabetes risk [45]. Although a handful of individual studies have failed to find an association between depression and incident diabetes [46–50], numerous meta-analyses of longitudinal studies have now been conducted on this topic, all of which have generated significant pooled risk estimates (ranging from RR=1.17 to RR=1.60 [40, 51–55]). These are listed in full in Table 1.2.

Following diabetes onset, depression has been significantly associated with many factors relating to diabetes control (e.g., hyperglycemia (standardized effect size=0.17 from meta-analyse of 24 studies)[56]), and diabetes self-management (e.g., diet nonadherence (OR=2.1), physical activity (OR=1.9), and smoking (OR=1.8) [57]. Depressed individuals are shown to have an increased tendency to skip blood glucose self-monitoring [58] and avoid medical appointments [59]. A large range of medical complications have also been linked to depression (e.g., both microvascular (HR=1.36) and macrovascular complications (HR=1.25) [12]) and increased risks of death have also been widely observed (HR=1.49 in a meta-analyses of 13 studies [60]. The medical consequences of comorbid depression and diabetes are described in more detail in Section 1.3.

Table 1.2: Summary of previously published meta-analyses on depression or anxiety and risk of incident diabetes

Author(s)	Year	No. of Studies	Publication Years of Included Studies	No. of Participants	Pooled Depression Risk Estimate	Pooled Anxiety Risk Estimate	Exclusion Criteria	
							Type 1 Diabetes[a]	Cross-Sectional[b]
Knol *et al.*	2006	9	1996 to 2004	174,035	RR: 1.37 (1.14, 1.63)	Not studied	YES	YES
Mezuk *et al.*	2008	13	1996 to 2007	222,019	RR: 1.60 (1.37, 1.88)	Not studied	YES	YES
Cosgrove *et al.*	2008	14	1997 to 2005	284,868	RR: 1.17 (1.05, 1.29)	Not studied	YES	YES
Hasan *et al.*[c]	2013	8	1999 to 2010	115,399	RR: 1.41 (1.13, 1.76)	Not studied	YES	YES
Hasan *et al.*[c]	2013	6	1999 to 2010	92,657	HR: 1.24 (1.05, 1.42)	Not studied	YES	YES
Rotella *et al.*	2013	23	1996 to 2011	424,557	HR: 1.38 (1.23, 1.55)	Not studied	NO	YES
Smith *et al.*	2013	12	2003 to 2011	12,626	Not studied	OR: 1.25 (1.10, 1.39)	NO	NO
Yu *et al.*	2015	20	1991 to 2012	2,411,641	RR: 1.32 (1.18, 1.47)	Not studied	YES	NO

[a] Excluded studies that examined incident Type 1 diabetes from risk estimate

[b] Excluded cross-sectional study designs

[c] Study calculated two pooled estimates (separately for point estimates and time-to-event)

1.1.2 Anxiety and Type 2 diabetes

Likewise, anxiety disorders occur at high rates in diabetic populations, with prevalence estimates ranging anywhere from 14.0 to 21.0% [38, 61]. Additionally, up to 40% of patients with diabetes have heightened subthreshold anxiety symptoms [61]. The most common type of anxiety that is associated with medical illness is generalized anxiety disorder (GAD) [62], and much of the research efforts in the area of medical comorbidities (i.e., cardiovascular disease, cancer, and diabetes) have focused on this disorder. Although the available body of research is smaller than that related to depression and tends to be more mixed, there is evidence that anxiety is associated with most of the major stages of the diabetes continuum. A handful of studies have demonstrated higher risks of diabetes in individuals with baseline anxiety (RR=2.19 [63] and OR=2.13 [64], while other studies have found mixed or no associations [65, 66]. As with depression, the risk of progression from prediabetes to diabetes is demonstrated to be much higher in individuals with anxiety than in non-anxious individuals (OR=8.95 versus OR=4.20) [45]. In a meta-analysis of studies that determined anxiety from diagnostic interviews, anxiety was also associated with hyperglycemia (pooled effect size=0.25) [67]. Recent research suggests that while anxiety is associated with measures of self-care such as poor diet adherence (OR=2.71), it is not associated with other measures such as monitoring blood glucose, smoking, and physical activity in the same sample [68]. Anxiety disorders have also been associated with diabetes complications in a hospital-based sample of diabetes patients (β=0.17) [69]. To our knowledge, no studies to date have examined the effect of anxiety on mortality in individuals with diabetes.

Anxiety disorders therefore represent a major comorbidity that remains understudied in diabetic populations, despite their strong independent association with depression. Generalized anxiety disorder, in particular, is strongly comorbid with (and commonly precedes) major depression [70].

Due to their closely related nature, some theories hypothesize a continuum of illness whereby depression and anxiety constitute different phenotypic expressions of the same neurobiological origin [70]. Despite observations that they likely share a common cause and are not usually present as independent disorders, the secondary presence of anxiety is very rarely accounted for in research studies examining the effects of depression. A recent commentary has offered the following explanations as to why anxiety disorders are frequently under-recognized, under researched, and overlooked as serious mental health problems [71]: first, it may be due to the misconception that anxiety disorders only occur amongst the "worried well", and are more representative of a personality trait than a disorder. Second, despite the fact that many anxiety disorders are relatively stable chronic conditions, societal impressions regarding the transient nature of fear during childhood may lead to a misconception that time or maturation will be enough to cure the symptoms. And lastly, the fact that anxiety itself is a normal emotion might make it challenging for many individuals to perceive the difference between normal and pathological fear and anxiety.

As can be seen in the diagnostic criteria listed in Table 1.1, major depression and generalized anxiety disorder share four common symptoms (according to DSM-V criteria). They are also characterized by heterogenous symptoms that may act in direct opposition to one other (e.g., insomnia versus hypersomnia, restlessness versus motor retardation). Anxiety is unique in that some of its symptoms may even confer protective benefits. Anxiety has been associated with low blood pressure (hypotension) in a large community-based sample of individuals (N=60,700) [72]. Although there is some evidence that hypotension may be associated with somatic and psychological symptoms [73, 74], it has traditionally been regarded as beneficial or a sign of non-disease. Anxiety has also been demonstrated to have a U-shaped relationship with mortality, with the highest mortality rates occurring in those with the lowest anxiety symptom loads, and the

presence of some anxiety symptoms reducing mortality risk [75]. It has been suggested that while anxiety might result in relative short-term increases in morbidity, it may actually confer long-term advantages against mortality. As observed by Deschenes *et al.*, it is therefore unclear if depressive symptoms and anxious symptoms have similar patterns of association with diabetes [45] .

1.1.2 Concurrent depression-anxiety and Type 2 diabetes

A wide range of data indicate that comorbid anxiety-depression is more common than either disorder alone, with as many as 50-75% of individuals diagnosed with major depression in a primary care setting also being diagnosed with a concurrent anxiety disorder [76, 77]. Psychiatric patients with comorbid depression-anxiety have a much poorer prognosis than depression alone, with greater severity of symptoms and more functional impairment [78]. These patients are also more difficult to treat, and require longer time to remission and need for increased medication [76].

A substantial body of research has provided evidence for robust associations between comorbid depression and anxiety and other chronic health outcomes, such as chronic obstructive pulmonary disease [79], cancer [80], and cardiovascular disease [80–82]. Mental health comorbidities in cardiovascular disease have generated the most research attention to date, demonstrating that the prevalence of depression or anxiety in these patients is at least three times higher than in the general population [82]. Furthermore, persistent depression and anxiety may substantially increase the risk of death in patients with ischemic heart disease [83]. Heart rate variability (a robust predictor of cardiac mortality) is shown to be reduced in individuals with major depression, and even greater reductions are observed in individuals with concurrent generalized anxiety disorder [84]. Alone, clinically diagnosed anxiety has been found to more than double the odds of subsequent coronary heart disease and acute myocardial infarction in Swedish men [85]. Other research investigating

symptoms of depression and anxiety as predictors of cardiovascular events (i.e., stroke, myocardial infarction, or heart failure) in adult women found that depression was a significant predictor of cardiovascular events among women with low anxiety scores (HR=2.3), but not high anxiety (HR=0.99) [86]; the authors suggest that the clinical utility of depression measures may therefore be improved by using them in conjunction with measures of anxiety [86].

It is worth noting that, while most people with depression also suffer from anxiety disorders, many of those experiencing anxiety do not suffer from depression [87]. The National Comorbidity Study (a large epidemiological study) showed that 20% of people with lifetime generalized anxiety disorder retrospectively report major depression, while 67% of those with major depression retrospectively report generalized anxiety [88]. Rates of comorbid depression-anxiety are reported as being three times higher in diabetic patients than healthy controls (i.e., 21.0% versus 7.3%) [38]. Much of the comorbidity between these conditions appears to stem from the diagnostic overlap of symptoms described in Table 1.1, meaning that individuals endorsing only depression (or only anxiety) symptoms may be experiencing very different psychopathologies from one another. This highlights the importance of efforts to detect and screen for anxiety disorders individually in addition to depression [87]. Despite the fact that this is the most common presentation of either disorder, even fewer studies have examined the impact of concurrent depression-anxiety on Type 2 diabetes outcomes than have looked at anxiety alone. However, research has demonstrated that individuals with diabetes and concurrent depression-anxiety appear to have higher odds of disability (OR=4.17) than either major depression (OR=2.79) or generalized anxiety (OR=3.69) alone [89]. A recent study also found co-occurring depression-anxiety to be more strongly associated with self-care outcomes (e.g., smoking (OR=1.90) and diet adherence (OR=3.39)) than either depression or anxiety alone [68].

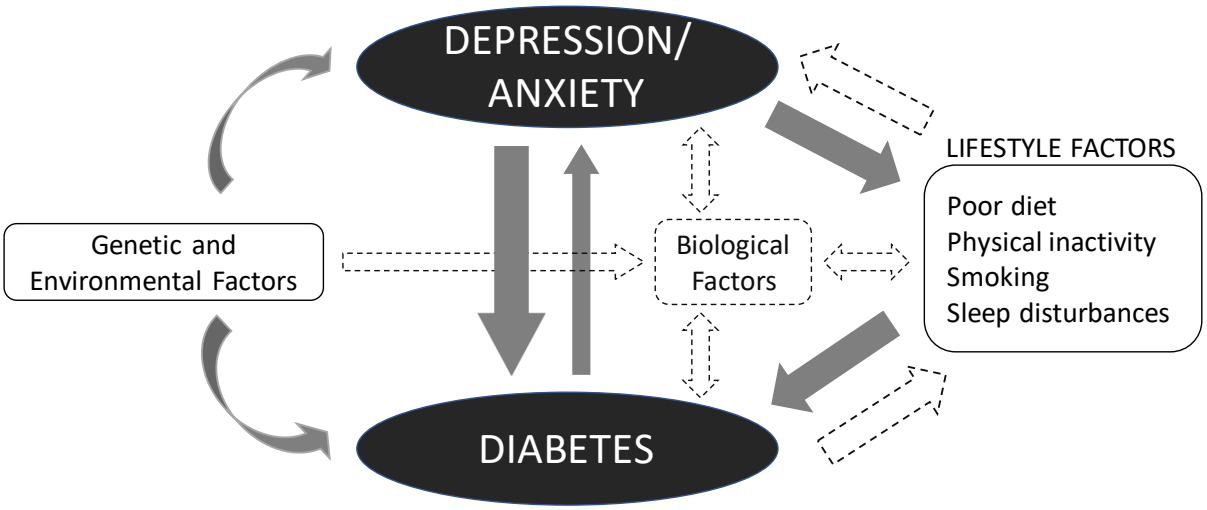
1.2 Potential mechanisms linking depression, anxiety, and Type 2 diabetes

As previously mentioned, Type 2 diabetes is a heterogenous disorder caused by a combination of genetic, behavioural, and environmental factors. As such, several plausible pathways have been developed in the literature to explain the associations between depression, anxiety and diabetes. The proposed mechanisms work through intermediary factors that can broadly be defined as behavioural or biological in nature, and are discussed under these headings in more detail below.

1.2.1 Behavioural Mechanisms

Depression and anxiety are associated with a number of lifestyle factors, including unhealthy eating [90], reduced physical activity [91], increased smoking [92], and irregular sleep patterns [93]. These may act as mediating factors in the relationship between depression and diabetes onset, as illustrated in Figure 1.2. The solid arrows in this figure represent relationships discussed in this section. The dotted arrows represent additional relationships established in the literature, and form an important part of the overall model of diabetes risk.

The association between poor diet, obesity and Type 2 diabetes onset has been recognized for decades [94]. Depression is associated with higher consumption of processed or fried foods, sugary products and simple carbohydrates [90], and it has been theorized that high fat foods may be used by depressed individuals as a form of self-medication or attempt to balance neurotransmitters involved in the regulation of mood [95]. These poor diets may lead to weight gain and visceral obesity, increasing the concentration of adipose tissue in the body and engendering insulin resistance through a series of complex mechanisms [94]. Anxiety is less strongly associated with diet [90] or body mass index (BMI) in the literature [96], and has been demonstrated as having a



Pathological Mechanisms

- Depression triggers ↑ intake of fats and sugars → visceral obesity → insulin resistance → diabetes
- Lethargy or anhedonia → physical inactivity → weight gain → ↓ vascular function, ↑ inflammation
- Smoking = ↑ oxidative stress and ↓insulin action → diabetes
- Insomnia or hypersomnia → altered sleep cycle chemistry → changes to insulin regulation

Figure 1.2: Potential behavioural mechanisms linking depression and anxiety to diabetes outcomes

potentially inverted U-shaped association with BMI (with higher anxiety scores occurring with medium BMI indices) [97].

Physical inactivity has simultaneous effects on weight gain [98], vascular function [99], and increased inflammatory responses in the body [100], all of which can be diabetogenic. Depressed and anxious individuals are shown to be more sedentary and exercise less than their counterparts in numerous studies [91], with fatigue and loss of energy being common symptoms of both disorders. Conversely, exercise is a modifiable factor that is known to reduce depression and anxiety [101, 102], as well as to have beneficial effects on multiple diabetes risk factors. Exercise has been suggested as a tool to improve the mood of patients and thereby help them to manage their medical problems more effectively [103]. While exercise can have positive chronic

influences on individuals who already have diabetes, it also activates acute fluctuations in glucose concentrations, and should therefore only be undertaken after consultation with a healthcare professional in more severe diabetes cases [104].

Smoking is a known risk factor for diabetes and other cardiovascular diseases [105], and is thought to exert deleterious effects on health through increases in oxidative stress and inflammation [106]. The activation of these processes has been shown to mediate insulin resistance and β-cell dysfunction [107, 108]. Individuals with depression and anxiety are far more likely to smoke, to smoke with higher intensity and frequency, and to have lower success at quitting than those without [109]. Interestingly, research suggests that previous studies may have overestimated the association between depression and smoking when ignoring comorbid symptoms of anxiety [92]. A large population-based study found that associations with smoking were strongest in participants with comorbid depression-anxiety, followed by anxiety, and only marginal in depression [92].

Sleep represents a physiologic state of decreased metabolism, characterized by reduced glucose turnover in metabolically active tissues (particularly during REM sleep) [110]. Disordered sleep is therefore associated with metabolic disturbances, and has been associated with both the incidence and the prevalence of Type 2 diabetes [111]. There are well-established links in the literature between sleep problems and both depression [112, 113] and anxiety [114], and it has been estimated that up to 90% of patients diagnosed with depression complain of insomnia or poor sleep quality [112].

In addition to the diabetogenic processes pictured above, depression and anxiety may exert their worst effects on individuals who already have diabetes, leading to higher risks of diabetes complications. Depression and anxiety may be associated with elements of diabetes self-care (e.g.,

compliance with medical treatment or glucose monitoring at home), and diabetic individuals who are depressed may manage their condition less actively [29]. One meta-analysis demonstrated that, compared with non-depressed patients, depressed patients have a three-fold increase in odds of noncompliance with medical treatment recommendations [115]. No relationship between anxiety and noncompliance was observed in the same study [115]. Depression is also demonstrated to be associated with significantly poorer participation in diabetes education programs [116], and there is even evidence that the relationship between depressive symptoms and the physical symptoms of poor glucose control may be entirely mediated by self-care [117].

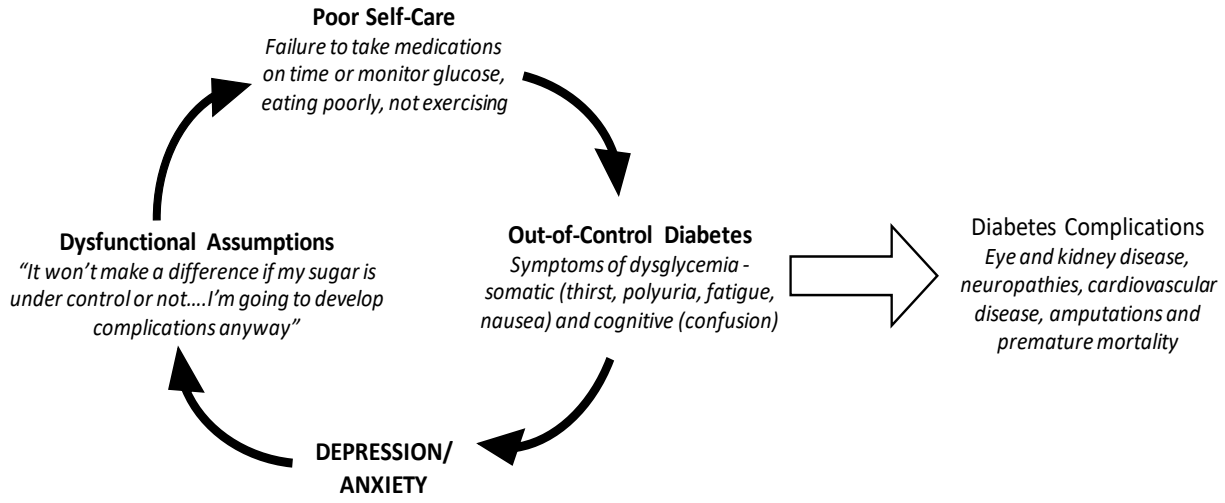


Figure 1.3: Cyclical relationship between depression and anxiety and poor diabetes control

A possible explanation for these observations is that certain behavioural (e.g., fatigue, loss of energy) or cognitive (e.g., diminished concentration, reduced decision-making abilities, dysfunctional assumptions) aspects of depression or anxiety may impede the undertaking of self-care activities. This could in turn result in poorer diabetes outcomes (including somatic and cognitive symptoms of dysglycemia). These symptoms could go on to trigger increases in or

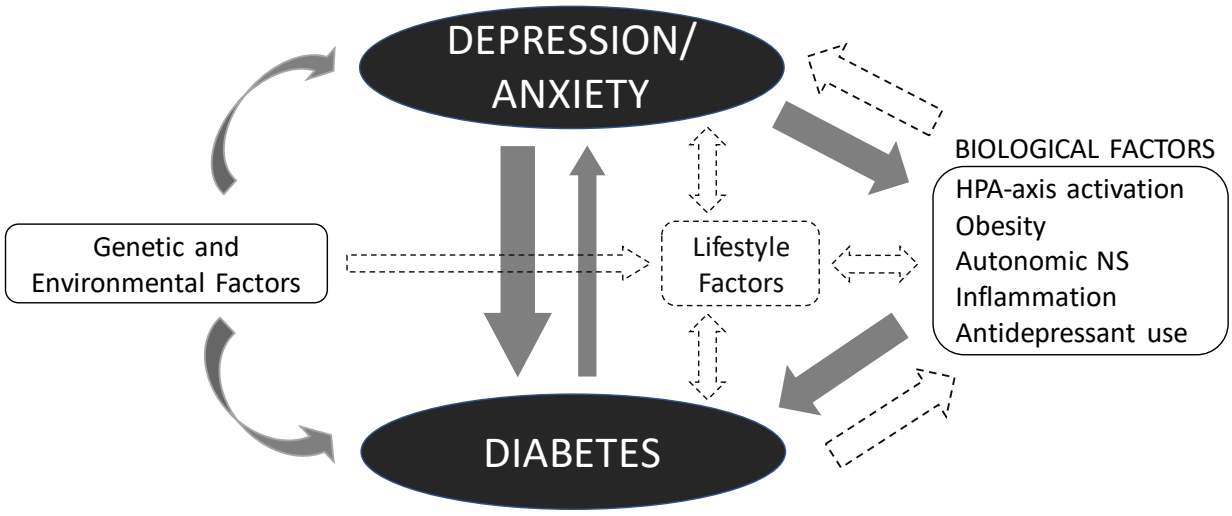
persistence of depressive or anxious symptoms, as well as ultimately increasing the overall risk of developing diabetes complications. A model of this cyclical relationship is given in Figure 1.3.

There is therefore ample evidence that depression and anxiety could work through behavioural and lifestyle factors to increase an individual's rate of progression to diabetes or its complications. Many of the behavioural factors discussed here ultimately elicit their effects on insulin action and diabetes onset by activating biological pathways, which are detailed in the following section.

1.2.2 Biological mechanisms

Given that diabetes is an endocrinological disease, biological pathways necessarily describe the most proximal stages of disease onset. Figure 1.4 depicts the same set of relationships introduced in the previous section, but this time focuses in on biological factors and the mechanisms through which depression and anxiety may influence diabetes outcomes.

Diabetes has been associated with hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis, which stimulates the release of corticotropin releasing hormone [118] and the subsequent increased secretion of glucocorticoids [119], a group of hormones that are involved in glucose metabolism. Cortisol is an important and ubiquitous glucocorticoid, and glucose metabolism can be highly sensitive to cortisol excesses, with chronic hypercortisolemia resulting in insulin resistance [29]. A similar HPA-axis response during depression has been one of the most consistent findings of biological psychiatry over the last 40 years [120], and many antidepressants are known to directly regulate HPA-axis functioning [121]. Depressed patients are also demonstrated to have elevated cortisol levels during the recovery period following exposure to



Pathological Mechanisms

- HPA axis activation stimulates ↑ glucocorticoids → insulin resistance → diabetes
- Obesity → ↑ plasma glucose, ↑ free fatty acid levels → insulin resistance
- Autonomic nervous system dysfunction → vascular and digestive dysfunction → insulin resistance
- Innate inflammatory response → pancreatic β-cell apoptosis → insulin resistance → diabetes
- Antidepressants → weight gain and disruption of glucose homeostasis → diabetes

Figure 1.4: Potential biological mechanisms linking depression and anxiety to diabetes outcomes

psychological stressors than non-depressed counterparts [122], and it has been suggested that this may have important implications for the way diabetic individuals cope with challenging or stressful situations [119]. The evidence linking anxiety to elevated cortisol levels is more mixed, with some studies suggesting modest or no effect in the absence of depression [123, 124].

As mentioned in Section 1.2.1, obesity is often a consequence of poor diet and physical inactivity, and represents one of the strongest risk factors for Type 2 diabetes in the literature. It is a major factor in insulin resistance, which may appear very early in the development of obesity and long before the appears of Type 2 diabetes [125]. A higher-than normal concentration of adipose tissue in the body leads to elevated plasma glucose, triggering subsequent rises in insulin levels. This is

a healthy compensatory mechanism for maintaining glycemic control [125], but in a persistent state will lead to insulin resistance [94]. In addition, the permanently elevated concentrations of plasma free fatty acids (FFAs) associated with obesity represent a major risk factor for insulin resistance [125]. Meta-analysis confirms a reciprocal link between obesity and depression [126], through many of the behavioural pathways discussed earlier. The evidence for a relationship between anxiety and obesity remains mixed, and some research has found that depression is associated with abdominal obesity in people with diabetes, while anxiety is not [127].

A third potential pathway to diabetes onset is via the autonomic nervous system. The autonomic nervous system controls many basic functions, including heart rate, breathing, digestion, and body temperature. Autonomic nervous system dysfunction (such as low heart rate variability, digestive difficulties, sweating abnormalities, or urinary problems) has been associated with the development of diabetes in healthy adults, as well as with fasting insulin and glucose levels independent of clinically diagnosed diabetes [128]. Depression is associated with markers of autonomic nervous system dysfunction [129], and research suggests that altered autonomic control of the heart could be one of the main links between psychological factors and hypertension [130]. Interestingly, the latter study tested a range of autonomic parameters in a clinic setting and concluded that anxiety could play a more important role in the development of hypertension than depression [130].

As mentioned previously, inflammation is suggested to play a crucial intermediary role in the pathogenesis of diabetes [4] [131]. The most common inflammatory markers include c-reactive protein (CRP), tumour necrosis factor (TNF-α), and interleukins 1 and 6 (IL-1 and IL-6). Meta-analysis has demonstrated an increased risk of diabetes associated with CRP levels [4], and a significant dose-response relationship in diabetes risk with IL-6 [4]. Depression is consistently

associated with a wide variety inflammatory biomarkers in the literature [132], and inflammatory processes themselves have been shown to be strongly mediated by life stressors [133]. Previous researchers have noted the paucity of research on the relationship between anxiety and inflammation, and cite that anxiety may be an even stronger risk factor for inflammatory disorders than depression [134].

Lastly, medications for the treatment of depression and anxiety have been proposed as potential mediators of the relationship between psychological risk factors and diabetes onset. Antidepressants induce weight gain in a substantial proportion of patients [135], which has been shown to increase the risk of Type 2 diabetes in this population [136, 137]. However, the literature on this topic is inconsistent, and more recently appears to be linked to specific drug type. For example, while some classes of antidepressants increase weight gain and diabetes risk (e.g., paroxetine and amitriptyline), others are associated with weight loss ((e.g., fluoxetine, buproprione), or may actually reduce hyperglycemia and increase insulin sensitivity (e.g., desimaprine) [138][135]. Broadly, some research suggests that cognitive behavioural and selective serotonin reuptake inhibitor (SSRI) treatments may preferable for treating depressed diabetic patients and yield improvements in glycemic control, while tricyclic antidepressants may cause metabolic disruption [139]. Drug class therefore appears to be an important moderator of these relationships, and more research is needed regarding specific antidepressant drug subtypes and the subsequent risk of type 2 diabetes.

Many of the biological pathways discussed above are linked through a series of regulatory and counterregulatory feedback loops, and may also interact with one another in ways not described here. Again, while the evidence base surrounding these various pathways is substantial, much of the research conducted to date indicates that depression and anxiety increase the risk of diabetes

independently of these key lifestyle and biological factors. This suggests that mechanisms may also be operating in these associations which have not yet been considered.

1.3 Sex-based differences in depression, anxiety and Type 2 diabetes outcomes

Although the majority of research on diabetes and mental health comorbidities tends to report combined estimates for both sexes, interesting differences have been noted in the handful of studies reporting sex-stratified results. For example, some studies show that while prevalences of depression tend to be consistently higher in women [140], men who experience depression are more likely to report issues with glycemic control than depressed women [141]. An additional small clinic-based sample of diabetic patients found a stronger association between glycemic control and either anxious or depressive symptomatology in men compared to women [142]. Evidence also suggests that depression and anxiety differentially predict sex-specific cortisol responses to stress in the general population, with depressed men experiencing higher cortisol levels during stress and anxiety moderating this effect [143]. Conversely, depressed women tend to display lower, flatter cortisol response curves, with anxiety related to higher cortisol reactivity in these participants [143].

Interestingly, in co-ed populations, the literature often shows minimal or conflicting evidence for a longitudinal relationship between depression and hypoglycemia over time [144], and mixed evidence for the benefits on glycemic control following treatments for depression [145]. This has led researchers to seek to shed light on these discontinuities, often by questioning approaches to depression assessment and subsequent treatment approaches [146]. The present thesis posits that the underlying cause of these discrepancies may relate to sex-based differences in the relationship between depression and glycemic control. This is supported by a study using an all male sample

(i.e., US veterans) to look at the longitudinal effects of depression on glycemic control, which demonstrated significant longitudinal differences in HbA1c levels than normal controls [147]. It is unknown whether these differences in outcomes could stem from differences in self-management behaviours in depressed men versus depressed women, or whether these behaviours might be associated with specific depressive or anxious phenotypes and more severe symptom profiles.

1.4 Medical costs and consequences of depression and anxiety in Type 2 diabetes

As mentioned in Section 1.1, depression and anxiety have been linked to an increased risk of both morbidity and mortality in individuals with Type 2 diabetes. A meta-analysis of 27 studies found that depressed diabetic individuals are at higher risk of experiencing a range of severe outcomes including advanced microvascular complications (e.g. retinopathies, blindness, renal disease, foot ulcers, and amputations [12, 148]). Patients with high baseline Beck Depression Inventory scores are demonstrated to have 2.5-times the odds of developing diabetic retinopathy, and 3-times the odds of progressing to the more severe proliferative diabetic retinopathy, than non-depressed diabetic patients over 6 years [149]. Likewise, Novak and colleagues demonstrated an excess risk of incident chronic kidney disease in over 930,000 US veterans with diabetes associated comorbid depression, as well as an increased risk of all-cause mortality in these patients, compared with non-depressed patients [150]. The macrovascular complications of diabetes can be more serious, including myocardial infarction, stroke and other cardiovascular events, all of which are associated with depression in these individuals [151]. Depression and anxiety also have the potential to worsen the experience of having these complications, and has shown to increase reported pain severity experienced by patients with diabetic peripheral neuropathy [152].

One of the most serious consequences of these comorbidities is an increased risk of death. Depression is associated with increases in both all-cause mortality and death due to coronary heart disease in diabetic individuals across a number of studies [153] [154]. Major depression has been associated with a 2.3-fold increase in mortality in diabetic patients over 3 years after controlling for multiple other factors, with minor depression yielding a 1.7-fold increase in death in these patients [155]. There is less evidence for the influence of anxiety on mortality rates in diabetic individuals. Interestingly, however, some general population studies demonstrate a negative interaction between anxiety and depression and mortality (i.e., comorbid anxiety lowering mortality risk in depressed individuals). In one study examining the effects of anxiety and depression on mortality using data from a large general population sample, anxiety levels appeared to display a U-shape relationship with mortality and attenuate the effects of depression, indicating that moderate levels of anxiety may confer some protective benefits against mortality risk [156].

The greater severity of complications observed in diabetic individuals with comorbid depression translates directly into increased functional or work disability and increased medical service use [12]. Adults with diabetes and depression are more likely to lose >7 days of work per year [157], and have much higher odds of experiencing functional disabilities than either depression or diabetes alone [153, 157]. Consequently, they are also more likely to experience a poorer quality of life than the non-depressed [158]. Results from the WHO World Health Surveys, which included 60 countries around the world, demonstrate that depression produces greater decrements in functional health status compared with other chronic conditions (i.e., angina, arthritis, asthma, and diabetes) [159]. Furthermore, depression comorbid with any of the latter chronic conditions results in greater decrements in health than the comorbidity between two or more chronic conditions without depression, and this additive effect is substantially amplified in the specific

case of depression comorbid with diabetes [159]. The costs of depression in diabetic patients are estimated to be 51% higher in primary care and 73% higher in ambulatory care relative to non-depressed patients, even after adjustment for diabetes severity and medical comorbidity [160]. Ciechanowski *et al.* estimate that the overall costs in individuals with depression and diabetes are increased 2-fold compared to costs in those with diabetes alone [151]. Similar findings were reported by another large-scale study, which found that diabetic patients with depression reported higher diabetes-related costs ($3264 USD) and total medical costs ($19,298) than diabetic patients without depression ($1297 USD and $4819 USD, respectively) [161]. By increasing medical inpatient, ambulatory, and total health care costs, major depression in Type 2 diabetes accounts for a substantial proportion of the current global medical costs [151]. Conversely, research on the cost of treating depression in diabetic patients demonstrates that after receiving a systematic depression treatment, comorbid patients had spent on average $314 USD less in outpatient service costs, and gained an additional 61 days free of depression. After valuing each day lived free of depression at $10, the net economic benefit of the program was estimated at $952 [162]. Likewise, diabetic individuals in the Pathways depression intervention program demonstrated reduced 5-year mean costs of $3907 USD per person when compared to patients in usual care [163]. More recently, problem-solving therapy has been shown to stabilize glucose and cholesterol levels for individuals with depression or anxiety for up to four months, in a small study conducted in Mexico City [164]. A second randomized trial has recently demonstrated that telemedicine-delivered behaviour action therapy is successful at lowering mean HbA1c values in a small sample of depressed individuals with diabetes [165].

As psychiatric symptoms are a frequently neglected contributor to chronic complications in Type 2 diabetes, this area of research may still be relatively unknown to many healthcare practitioners.

It has been recommended that depression and self-care skills be addressed simultaneously to achieve optimal diabetes outcomes. The International Diabetes Federation and Diabetes Canada clinical practice guidelines both require periodic assessment and monitoring of patients with diabetes for depression and psychological distress [166, 167], and the integration of performance measures for depression into diabetes clinical guidelines has also been recommended [168]. Despite the widespread availability of effective screening tools, depression is frequently missed in diabetic patients, and research suggests that most health facilities are poorly equipped to deal with these comorbidities [169]. One of the barriers to early recognition of depression in patients with diabetes may in fact be the difficulty in differentiating between the symptom of depression and symptoms of poor disease management [168].

There is therefore considerable evidence for the functional impairment, costs, and adverse health outcomes associated with depression in diabetes. This increased risk is not limited to individuals with diagnosed major depression, but also extends to individuals with elevated symptoms in an incremental fashion [153]. As succinctly stated by Pirraglia *et al.*, depression in diabetes is 1) prevalent, 2) burdensome, 3) costly and 4) treatable [170]. What is currently less well known is whether the same can be said for anxiety or concurrent depression-anxiety. While a fair amount is known about how anxiety may act to worsen diabetes control and impede self-management in diabetic patients, it is clear that more epidemiologic and physiologic evidence is needed regarding the co-occurrence of these conditions, their etiology, and their population-level impacts. Given the highly shared symptomatology of depression and anxiety, previous research that has focused primarily on depression may be subject to important biases - excluding symptoms of anxiety could result in an over- or underestimation of the association between depression and diabetes outcomes, either of which may have important implications for diabetes management, prevention, and

treatment. Research is therefore needed that examines the effects of these respective comorbidities, preferably within the same study population, in order to clarify these relationships.

1.5 Purpose and objectives of the thesis

The overall objective of this thesis was to explore the independent and concurrent contributions of symptoms of depression and anxiety to key outcomes during major stages of the diabetes continuum, namely: Type 2 diabetes onset, diabetes management, and mortality (Figure 1.5).

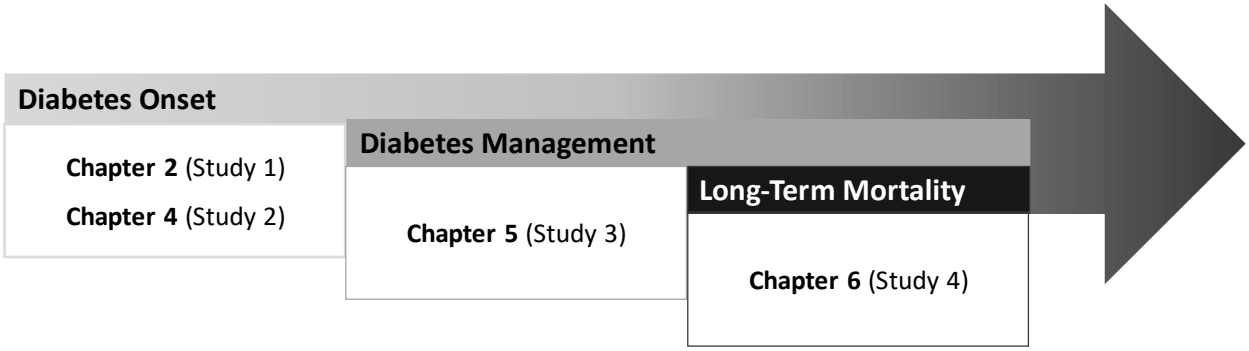


Figure 1.5: Dissertation studies grouped by stages along the diabetes continuum

Specifically, the aim of the study presented in Chapter 2 was to provide a comprehensive summary of the available research on depression, anxiety and concurrent depression-anxiety as risk factors for Type 2 diabetes onset. While multiple meta-analyses have estimated the pooled effect of depression on diabetes onset using longitudinal studies, no studies to our knowledge have estimated the equivalent pooled effect of anxiety or concurrent depression-anxiety on this association. More importantly, no meta-analyses have examined whether these longitudinal effects are independent of one another, or whether they are moderated by sex. In addition to addressing the preceding questions, this literature review may also help to identify possible gaps in the current

literature by summarizing the results over a range of relevant study features (e.g., adjustment for key covariates, duration of follow-up, and type of diagnostic tool used). The main study hypotheses were: 1) that the effect of depression on diabetes onset would be attenuated in studies controlling for concurrent symptoms of anxiety, and vice versa, and 2) that these associations with diabetes onset would be stronger in men than women.

The aim of the study presented in Chapter 4 was to examine the risk of diabetes onset associated with clusters of risk factors, including symptoms of depression, anxiety, and concurrent depression-anxiety, by calculating their respective population attributable fractions (PAFs) in a large general population sample. While PAFs have been used previously to estimate the proportion of cases attributable to traditional diabetes risk factors, this study may shed some light on the proportion of diabetes cases that are attributable to common psychological symptoms, both alone and in combination with other traditional risk factors. This novel approach may help to inform future prevention efforts by describing the population impact of different baseline combinations of modifiable risk factors on diabetes incidence, and help to target high-risk groups more effectively. The main study hypotheses were: 1) that symptoms of depression and anxiety would amplify the risk associated with traditional risk factors, and 2) that these effects on diabetes onset would be stronger in men than in women.

The aim of the study presented in Chapter 5 was to estimate the associations between these psychological exposures and a comprehensive range of key clinical and self-management outcomes, in a large community-based sample of individuals with Type 2 diabetes. This approach may help to identify important sub-groups of patients who are at risk of experiencing specific types of clinical outcomes, and who may require additional support in relation to specific aspects of diabetes self-management. While evidence exists for the relationship between many of these

outcomes and depression, and to a lesser extent anxiety, little research to date has examined concurrent depression-anxiety or attempted to control for the confounding presence of the other. In addition, prior studies have rarely explored sex-specific effects in these associations. This study may also help to identify potential mediational variables of these relationships, in more specific subgroups than have previously been explored. The main study hypotheses were: 1) that symptoms of depression, anxiety, and concurrent depression-anxiety would be independently associated with clinical indicators of poor glycemic control, 2) that this association would be stronger in men than in women, and 3) that symptoms of depression and anxiety would be differentially associated with self-management outcomes in both men and women.

And lastly, the aim of the study presented in Chapter 6 was to estimate the excess mortality risk associated with Type 2 diabetes and the above combinations of depressive and anxious symptoms over the long term. While prior studies have been conducted to estimate the effect of depression on mortality in Type 2 diabetes, these studies do not appear to account for potential confounding due to the presence of anxiety, and equivalent estimates have not been documented with respect to anxiety or concurrent depression-anxiety. Given the inconsistent relationship between anxiety and mortality in the general population, these exposures are of substantial interest. In addition, the effect of moderation by sex has not been explored in the above relationships. This study might provide a glimpse at the long-term profile of risk associated with baseline symptoms of depression and anxiety in individuals with Type 2 diabetes. The main study hypotheses were: 1) that mortality risk would be highest in individuals experiencing concurrent depression-anxiety than either disorder alone, and 2) that these risks would be higher in men than in women.

The specific research questions corresponding to each study are listed in Table 1.3.

Table 1.3: Research questions corresponding to the four thesis studies

Thesis Study	Research Questions
Chapter 2 (Study 1)	• Do major depression and generalized anxiety increase the risk of Type 2 diabetes onset in adults? • Are these effects independent of one another? • Are these effects independent of anti-depressant use? • Are these effects equal in men and women? • What is the joint effect of concurrent symptoms of depression and anxiety on Type 2 diabetes onset?
Chapter 4 (Study 2)	• What proportion of Type 2 diabetes cases are attributable to symptoms of depression and anxiety in a general population sample? • What proportion of Type 2 diabetes cases are attributable to concurrent depression and anxiety in the same sample? • Do specific combinations of known risk factors, in conjunction with symptoms of depression and anxiety, predict diabetes incidence more strongly than others? • What are the population attributable fractions for Type 2 diabetes associated with these risk factor combinations? • Are these attributable fractions equal in men and women?
Chapter 5 (Study 3)	• Are depression and anxiety differentially associated with key clinical outcomes in individuals with Type 2 diabetes? • Are symptoms of depression and anxiety differentially associated with key behavioural and self-management outcomes in individuals with Type 2 diabetes? • Are concurrent symptoms of depression-anxiety more strongly associated with the above outcomes? • Are these associations similar in men and women?
Chapter 6 (Study 4)	• What is the long-term risk of excess mortality associated with symptoms of depression or anxiety in individuals with and without Type 2 diabetes? • What is the long-term risk of excess mortality associated with concurrent depression and anxiety in individuals with and without Type 2 diabetes? • Are these associations similar in men and women?

REFERENCES

1. Whiting DR, Guariguata L, Weil C, Shaw J (2011) IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract 94:311–21. doi: 10.1016/j.diabres.2011.10.029

2. NCD Risk Factor Collaboration (NCD-RisC) NRFC (2016) Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. Lancet (London, England) 387:1513–30. doi: 10.1016/S0140-6736(16)00618-8

3. International Diabetes Federation (2015) IDF Diabetes Atlas, 7th Edition. International Diabetes Federation, Brussels, Belgium

4. Wang X, Bao W, Liu J, et al (2013) Inflammatory markers and risk of type 2 diabetes: a systematic review and meta-analysis. Diabetes Care 36:166–75. doi: 10.2337/dc12-0702

5. Ozougwu O, C. J, Obimba, et al (2013) The pathogenesis and pathophysiology of type 1 and type 2 diabetes mellitus. J Physiol Pathophysiol 4:46–57. doi: 10.5897/JPAP2013.0001

6. Chen L, Magliano DJ, Zimmet PZ (2011) The worldwide epidemiology of type 2 diabetes mellitus—present and future perspectives. Nat Rev Endocrinol 8:228–236. doi: 10.1038/nrendo.2011.183

7. Gonzalez ELM, Johansson S, Wallander M-A, Rodriguez LAG (2009) Trends in the prevalence and incidence of diabetes in the UK: 1996-2005. J Epidemiol Community Heal 63:332–336. doi: 10.1136/jech.2008.080382

8. Holt RIG (2004) Diagnosis, epidemiology and pathogenesis of diabetes mellitus: an update for psychiatrists. Br J Psychiatry Suppl 47:S55-63.

9. Schulze MB, Hu FB (2014) Epidemiology of Diabetes. In: Handb. Epidemiol. Springer New York, New York, NY, pp 2429–2467

10. Duckworth W, Abraira C, Moritz T, et al (2009) Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes. N Engl J Med 360:129–139. doi: 10.1056/NEJMoa0808431

11. de Groot M, Anderson R, Freedland KE, et al (2001) Association of depression and diabetes complications: a meta-analysis. Psychosom Med 63:619–30. doi: 10.1097/00006842-200107000-00015

12. Lin EHB, Rutter CM, Katon W, et al (2010) Depression and advanced complications of diabetes: a prospective cohort study. Diabetes Care 33:264–9. doi: 10.2337/dc09-1068

13. Stratton I, Adler A, Neil H (2000) Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. Bmj

14. Johnson JA, Carstensen B, Witte D, et al (2012) Diabetes and cancer (1): evaluating the temporal relationship between type 2 diabetes and cancer incidence. Diabetologia 55:1607–1618. doi: 10.1007/s00125-012-2525-1

15. Renders CM, Valk GD, Griffin SJ, et al (2001) Interventions to improve the management of diabetes in primary care, outpatient, and community settings: a systematic review. Diabetes Care 24:1821–33. doi: 10.2337/DIACARE.24.10.1821

16. Cheng AYY, Canadian Diabetes Association Clinical Practice Guidelines Expert Committee (2013) Canadian Diabetes Association 2013 clinical practice guidelines for the prevention and management of diabetes in Canada. Can J Diabetes 37:S1–S3. doi: 10.1016/j.jcjd.2013.01.009

17. Nash J (2014) Understanding the psychological impact of diabetes and the role of clinical psychology. J. Diabetes Nurs. 18:

18. Bradley SM, Rumsfeld JS (2015) Depression and cardiovascular disease. Trends Cardiovasc Med 25:614–22. doi: 10.1016/j.tcm.2015.02.002

19. Spiegel D, Giese-Davis J (2003) Depression and cancer: mechanisms and disease progression. Biol Psychiatry 54:269–282. doi: 10.1016/S0006-3223(03)00566-3

20. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ (2001) The Prevalence of Comorbid Depression in Adults With Diabetes: A meta-analysis. Diabetes Care 24:1069–1078. doi: 10.2337/diacare.24.6.1069

21. Goldenberg R, Punthakee Z, Grundy S, et al (2013) Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome. Can J Diabetes 37:S8–S11. doi: 10.1016/j.jcjd.2013.01.011

22. American Psychiatric Association., American Psychiatric Association. DSM-5 Task Force. (2013) Diagnostic and statistical manual of mental disorders : DSM-5. American Psychiatric Association, United States of America

23. World Health Organization (2016) Global Health Estimates 2015: Disease burden by Cause, Age, Sex, by Country and by Region, 2000-2015. Geneva

24. Kessler RC, Berglund P, Demler O, et al (2005) Lifetime Prevalence and Age-of-Onset Distributions of DSM-IV Disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 62:593. doi: 10.1001/archpsyc.62.6.593

25. Bandelow B, Michaelis S (2015) Epidemiology of anxiety disorders in the 21st century. Dialogues Clin Neurosci 17:327–35.

26. World Health Organization (2017) Depression and Other Common Mental Disorders: Global Health Estimates. Geneva

27. Mathers CD, Loncar D (2006) Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med 3:e442. doi: 10.1371/journal.pmed.0030442

28. Willis T (1971) Diabetes: a medical odyssey. New York, Tuckahoe

29. Rubin RR, Peyrot M (2002) Was Willis right? Thoughts on the interaction of depression and diabetes. Diabetes Metab Res Rev 18:173–175. doi: 10.1002/dmrr.292

30. Gendel BR, Benjamin JE (1946) Psychogenic Factors in the Etiology of Diabetes. N Engl J Med 234:556–560. doi: 10.1056/NEJM194604252341703

31. Joslin EP (1943) The relation of trauma to diabetes. Ann Surg 117:607–22.

32. Thomson V (1938) The History of Traumatic Diabetes. J Intern Med 95:9–36. doi: 10.1111/j.0954-6820.1938.tb11706.x

33. Menninger WC (1935) Psychological factors in the etiology of diabetes. J Nerv Ment Dis 81:1–13.

34. Daniels G (1948) The Role of Emotion in the Onset and Course of Diabetes. : Psychosomatic

Medicine. Psychosom Med 10:288–290.

35. Daniels G (1948) The psychosomatic approach in medical practice. Bull N Y Acad Med 24:209–26.

36. Daniels GE (1944) Brief Psychotherapy in Diabetes Mellitus. Psychiatry Interpers Biol Process 7:121–128. doi: 10.1080/00332747.1944.11022494

37. Ali S, Stone MA, Peters JL, et al (2006) The prevalence of co-morbid depression in adults with Type 2 diabetes: a systematic review and meta-analysis. Diabet Med 23:1165–1173. doi: 10.1111/j.1464-5491.2006.01943.x

38. Rajput R, Gehlawat P, Gehlan D, et al (2016) Prevalence and predictors of depression and anxiety in patients of diabetes mellitus in a tertiary care center. Indian J Endocrinol Metab 20:746–751. doi: 10.4103/2230-8210.192924

39. Engum A (2007) The role of depression and anxiety in onset of diabetes in a large population-based study. J. Psychosom. Res.

40. Mezuk B, Eaton W, Albrecht S, Golden S (2008) Depression and type 2 diabetes over the lifespan a meta-analysis. Diabetes Care

41. Kan C, Silva N, Golden SH, et al (2013) A systematic review and meta-analysis of the association between depression and insulin resistance. Diabetes Care 36:480–9. doi: 10.2337/dc12-1442

42. Khambaty T, Stewart JC, Muldoon MF, Kamarck TW (2014) Depressive symptom clusters as predictors of 6-year increases in insulin resistance: data from the Pittsburgh Healthy Heart Project. Psychosom Med 76:363–9. doi: 10.1097/PSY.0000000000000063

43. Federation ID (2015) International Diabetes Federation Atlas 2015. 7th Edition. Brussels, Belgium

44. Nathan DM, Davidson MB, DeFronzo RA, et al (2007) Impaired fasting glucose and impaired glucose tolerance: implications for care. Diabetes Care 30:753–9. doi: 10.2337/dc07-9920

45. Deschênes SS, Burns RJ, Graham E, Schmitz N (2016) Prediabetes, depressive and anxiety symptoms, and risk of type 2 diabetes: A community-based cohort study. J Psychosom Res 89:85–90. doi: 10.1016/j.jpsychores.2016.08.011

46. Bai Y-M, Su T-P, Chen M-H, et al (2013) Risk of developing diabetes mellitus and hyperlipidemia among patients with bipolar disorder, major depressive disorder, and schizophrenia: a 10-year nationwide population-based prospective cohort study. J Affect Disord 150:57–62. doi: 10.1016/j.jad.2013.02.019

47. Icks A, Albers B, Haastert B, et al (2013) Diabetes incidence does not differ between subjects with and without high depressive symptoms - 5-year follow-up results of the Heinz Nixdorf Recall Study. Diabet Med 30:65–69. doi: 10.1111/j.1464-5491.2012.03724.x

48. Gangwisch JE, Gross R, Malaspina D (2015) Differential Associations Between Depression, Risk Factors for Insulin Resistance and Diabetes Incidence in a Large U.S. Sample. Isr J Psychiatry Relat Sci 52:85–90.

49. Poulsen K, Cleal B, Clausen T, Andersen LL (2014) Work, Diabetes and Obesity: A Seven Year Follow-Up Study among Danish Health Care Workers. PLoS One 9:e103425. doi: 10.1371/journal.pone.0103425

50. van den Akker M, Schuurman A, Metsemakers J, Buntinx F (2004) Is depression related to subsequent diabetes mellitus? Acta Psychiatr Scand 110:178–183. doi: 10.1111/j.1600-

0447.2004.00333.x

51. Knol MJ, Twisk JWR, Beekman ATF, et al (2006) Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. Diabetologia 49:837–845. doi: 10.1007/s00125-006-0159-x

52. Cosgrove MP, Sargeant LA, Griffin SJ (2008) Does depression increase the risk of developing type 2 diabetes? Occup Med (Chic Ill) 58:7–14. doi: 10.1093/occmed/kqm105

53. Hasan SS, Clavarino AM, Mamun AA, et al (2013) Population impact of depression either as a risk factor or consequence of type 2 diabetes in adults: A meta-analysis of longitudinal studies. Asian J Psychiatr 6:460–472. doi: 10.1016/j.ajp.2013.09.008

54. Rotella F, Mannucci E (2013) Diabetes mellitus as a risk factor for depression. A meta-analysis of longitudinal studies. Diabetes Res Clin Pract 99:98–104. doi: 10.1016/j.diabres.2012.11.022

55. Yu M, Zhang X, Lu F, Fang L (2015) Depression and Risk for Diabetes: A Meta-Analysis. Can J Diabetes 39:266–272. doi: 10.1016/j.jcjd.2014.11.006

56. Lustman PJ, Anderson RJ, Freedland KE, et al (2000) Depression and Poor Glycemic Control: A meta-analytic review of the literature. Diabetes Care 23:934–942.

57. Lin E, Katon W, Korff M Von (2004) Relationship of depression and diabetes self-care, medication adherence, and preventive care. Diabetes Care 27:

58. Wagner JA, Tennen H, Osborn CY (2010) Lifetime depression and diabetes self-management in women with Type 2 diabetes: a case-control study. Diabet Med 27:713–7. doi: 10.1111/j.1464-5491.2010.02996.x

59. Gonzalez JS, Peyrot M, McCarl LA, et al (2008) Depression and diabetes treatment nonadherence: a meta-analysis. Diabetes Care 31:2398–403. doi: 10.2337/dc08-1341

60. van Dooren FEP, Nefs G, Schram MT, et al (2013) Depression and risk of mortality in people with diabetes mellitus: a systematic review and meta-analysis. PLoS One 8:e57058. doi: 10.1371/journal.pone.0057058

61. Grigsby AB, Anderson RJ, Freedland KE, et al (2002) Prevalence of anxiety in adults with diabetes: a systematic review. J Psychosom Res 53:1053–60.

62. Fava GA, Porcelli P, Rafanelli C, et al (2010) The Spectrum of Anxiety Disorders in the Medically Ill. J Clin Psychiatry 71:910–914. doi: 10.4088/JCP.10m06000blu

63. Demmer RT, Gelb S, Suglia SF, et al (2015) Sex differences in the association between depression, anxiety, and type 2 diabetes mellitus. Psychosom Med 77:467–77. doi: 10.1097/PSY.0000000000000169

64. Hasan SS, Clavarino AM, Mamun AA, Kairuz T (2016) Anxiety symptoms and the risk of diabetes mellitus in Australian women: evidence from 21-year follow-up. Public Health 130:21–28. doi: 10.1016/j.puhe.2015.07.022

65. Abraham S, Shah NG, Diez Roux A, et al (2015) Trait anger but not anxiety predicts incident type 2 diabetes: The Multi-Ethnic Study of Atherosclerosis (MESA). Psychoneuroendocrinology 60:105–13. doi: 10.1016/j.psyneuen.2015.06.007

66. Edwards LE, Mezuk B (2012) Anxiety and risk of type 2 diabetes: evidence from the Baltimore Epidemiologic Catchment Area Study. J Psychosom Res 73:418–23. doi: 10.1016/j.jpsychores.2012.09.018

67. Anderson RJ, Grigsby AB, Freedland KE, et al (2002) Anxiety and Poor Glycemic Control: A Meta-Analytic Review of the Literature. Int J Psychiatry Med 32:235–247. doi: 10.2190/KLGD-4H8D-4RYL-TWQ8

68. Smith KJ, Pedneault M, Schmitz N (2016) Investigation of anxiety and depression symptom co-morbidity in a community sample with type 2 diabetes: Associations with indicators of self-care. Can J Public Health 106:e496-501.

69. Wu S-FV, Huang Y-C, Liang S-Y, et al (2011) Relationships among depression, anxiety, self-care behaviour and diabetes education difficulties in patients with type-2 diabetes: a cross-sectional questionnaire survey. Int J Nurs Stud 48:1376–83. doi: 10.1016/j.ijnurstu.2011.04.008

70. Baldwin DS, Evans DL, Hirschfeld RMA, Kasper S (2002) Can we distinguish anxiety from depression? Psychopharmacol Bull 36 Suppl 2:158–65.

71. Hudson JL (2017) Prevention of Anxiety Disorders Across the Lifespan. JAMA Psychiatry. doi: 10.1001/jamapsychiatry.2017.2430

72. Hildrum B, Mykletun A, Stordal E, et al (2007) Association of low blood pressure with anxiety and depression: the Nord-Trøndelag Health Study. J Epidemiol Community Health 61:53–8. doi: 10.1136/jech.2005.044966

73. Rosengren A, Tibblin G, Wilhelmsen L (1993) Low systolic blood pressure and self perceived wellbeing in middle aged men. BMJ 306:243–6.

74. Wessely S, Nickson J, Cox B Symptoms of low blood pressure: a population study. BMJ 301:362–5.

75. Mykletun A, Bjerkeset O, Overland S, et al (2009) Levels of anxiety and depression as predictors of mortality: the HUNT study. Br J Psychiatry 195:118–25. doi: 10.1192/bjp.bp.108.054866

76. Hirschfeld R (2001) The comorbidity of major depression and anxiety disorders: recognition and management in primary care. Prim. care companion to J. Clin. …

77. Olfson M, Fireman B (1997) Mental disorders and disability among patients in a primary care group practice. Am. J. …

78. Löwe B, Spitzer RL, Williams JBW, et al (2008) Depression, anxiety and somatization in primary care: syndrome overlap and functional impairment. Gen Hosp Psychiatry 30:191–9. doi: 10.1016/j.genhosppsych.2008.01.001

79. Yohannes AM, Willgoss TG, Baldwin RC, Connolly MJ (2010) Depression and anxiety in chronic heart failure and chronic obstructive pulmonary disease: prevalence, relevance, clinical implications and management principles. Int J Geriatr Psychiatry 25:1209–1221. doi: 10.1002/gps.2463

80. Clarke DM, Currie KC (2009) Depression, anxiety and their relationship with chronic diseases: a review of the epidemiology, risk and treatment evidence. Med J Aust 190:S54-60.

81. Pan X-F, Meng R, Liu N, Pan A (2017) Depression, Anxiety, and Cardiovascular Disease in Chinese: A Review for a Bigger Picture. Cardiovasc Innov Appl 2:237–251. doi: 10.15212/CVIA.2016.0059

82. Cohen BE, Edmondson D, Kronish IM (2015) State of the Art Review: Depression, Stress, Anxiety, and Cardiovascular Disease. Am J Hypertens 28:1295–1302. doi: 10.1093/ajh/hpv047

83. Doering L V., Moser DK, Riegel B, et al (2010) Persistent comorbid symptoms of depression and

anxiety predict mortality in heart disease. Int J Cardiol 145:188–192. doi: 10.1016/j.ijcard.2009.05.025

84. Kemp AH, Quintana DS, Felmingham KL, et al (2012) Depression, Comorbid Anxiety Disorders, and Heart Rate Variability in Physically Healthy, Unmedicated Patients: Implications for Cardiovascular Risk. PLoS One 7:e30777. doi: 10.1371/journal.pone.0030777

85. Janszky I, Ahnve S, Lundberg I, Hemmingsson T (2010) Early-Onset Depression, Anxiety, and Risk of Subsequent Coronary Heart Disease. J Am Coll Cardiol 56:31–37. doi: 10.1016/j.jacc.2010.03.033

86. Rutledge T, Linke SE, Krantz DS, et al (2009) Comorbid depression and anxiety symptoms as predictors of cardiovascular events: results from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) study. Psychosom Med 71:958–64. doi: 10.1097/PSY.0b013e3181bd6062

87. Hamelsky SW, Lipton RB (2006) Psychiatric comorbidity of migraine. Headache 46:1327–33. doi: 10.1111/j.1526-4610.2006.00576.x

88. Kessler RC, DuPont RL, Berglund P, Wittchen HU (1999) Impairment in pure and comorbid generalized anxiety disorder and major depression at 12 months in two national surveys. Am J Psychiatry 156:1915–23. doi: 10.1176/ajp.156.12.1915

89. Deschênes SS, Burns RJ, Schmitz N (2015) Associations between diabetes, major depressive disorder and generalized anxiety disorder comorbidity, and disability: Findings from the 2012 Canadian Community Health Survey — Mental Health (CCHS-MH). J Psychosom Res 78:137–142. doi: 10.1016/j.jpsychores.2014.11.023

90. Jacka FN, Pasco JA, Mykletun A, et al (2010) Association of Western and Traditional Diets With Depression and Anxiety in Women. Am J Psychiatry 167:305–311. doi: 10.1176/appi.ajp.2009.09060881

91. Mutrie N (2001) The relationship between physical activity and clinically defined depression. Phys Act Psychol well-being 46–62.

92. Mykletun A, Overland S, Aarø LE, et al (2008) Smoking in relation to anxiety and depression: evidence from a large population survey: the HUNT study. Eur Psychiatry 23:77–84. doi: 10.1016/j.eurpsy.2007.10.005

93. Brunello N, Armitage R, Feinberg I, et al (2000) Depression and sleep disorders: clinical relevance, economic burden and pharmacological treatment. Neuropsychobiology 42:107–19. doi: 26680

94. Kahn BB, Flier JS (2000) Obesity and insulin resistance. J Clin Invest 106:473–81. doi: 10.1172/JCI10842

95. Bruinsma K, Taren DL, Rudin R., et al (1999) Chocolate: Food or Drug? J Am Diet Assoc 99:1249–1256. doi: 10.1016/S0002-8223(99)00307-7

96. Bjørngaard JH, Carslake D, Lund Nilsen TI, et al (2015) Association of Body Mass Index with Depression, Anxiety and Suicide—An Instrumental Variable Analysis of the HUNT Study. PLoS One 10:e0131708. doi: 10.1371/journal.pone.0131708

97. Haghighi M, Jahangard L, Ahmadpanah M, et al (2016) The relation between anxiety and BMI – is it all in our curves? Psychiatry Res 235:49–54. doi: 10.1016/j.psychres.2015.12.002

98. Hill J (2004) Physical activity and obesity. Lancet (London, England) 363:182. doi: 10.1016/S0140-6736(03)15368-8

99. Nosova E V, Yen P, Chong KC, et al (2014) Short-term physical inactivity impairs vascular function. J Surg Res 190:672–82. doi: 10.1016/j.jss.2014.02.001

100. Fischer CP, Berntsen A, Perstrup LB, et al (2006) Plasma levels of interleukin-6 and C-reactive protein are associated with physical inactivity independent of obesity. Scand J Med Sci Sport 0:061120070736003–??? doi: 10.1111/j.1600-0838.2006.00602.x

101. Strawbridge WJ, Deleger S, Roberts RE, Kaplan GA (2002) Physical Activity Reduces the Risk of Subsequent Depression for Older Adults. Am J Epidemiol 156:328–334. doi: 10.1093/aje/kwf047

102. Ströhle A (2009) Physical activity, exercise, depression and anxiety disorders. J Neural Transm 116:777–784. doi: 10.1007/s00702-008-0092-x

103. Steptoe A Depression and physical activity. In: Steptoe A (ed) Depress. Phys. Illn. Cambridge University Press, Cambridge, pp 348–368

104. Chipkin SR, Klugh SA, Chasan-Taber L (2001) Exercise and diabetes. Cardiol Clin 19:489–505.

105. Haire-Joshu D, Glasgow RE, Tibbs TL (1999) Smoking and diabetes. Diabetes Care 22:1887–98. doi: 10.2337/DIACARE.22.11.1887

106. Agarwal R (2005) Smoking, oxidative stress and inflammation: Impact on resting energy expenditure in diabetic nephropathy. BMC Nephrol 6:13. doi: 10.1186/1471-2369-6-13

107. Evans JL, Goldfine ID, Maddux BA, Grodsky GM (2003) Are oxidative stress-activated signaling pathways mediators of insulin resistance and beta-cell dysfunction? Diabetes 52:1–8. doi: 10.2337/DIABETES.52.1.1

108. Manzella D, Barbieri M, Ragno E, Paolisso G (2001) Chronic administration of pharmacologic doses of vitamin E improves the cardiac autonomic nervous system in patients with type 2 diabetes. Am J Clin Nutr 73:1052–7.

109. Trosclair A, Dube SR (2010) Smoking among adults reporting lifetime depression, anxiety, anxiety with depression, and major depressive episode, United States, 2005–2006. Addict Behav 35:438–443. doi: 10.1016/j.addbeh.2009.12.011

110. Joo EY (2016) Sleep and Diabetes. J Korean Diabetes 17:155. doi: 10.4093/jkd.2016.17.3.155

111. Hernandez A, Philippe J, Jornayvaz FR (2012) Sleep and diabetes. Rev Med Suisse 8:1198–200, 1202–3.

112. Tsuno N, Besset A, Ritchie K (2005) Sleep and Depression. J Clin Psychiatry 66:1254–1269. doi: 10.4088/JCP.v66n1008

113. Sivertsen B, Salo P, Mykletun A, et al (2012) The Bidirectional Association Between Depression and Insomnia. Psychosom Med 74:758–765. doi: 10.1097/PSY.0b013e3182648619

114. Bartoli AJ, Gregory AM (2017) Sleep and Anxiety. In: Wiley Handb. Dev. Psychopathol. John Wiley & Sons, Ltd, Chichester, UK, pp 215–232

115. DiMatteo MR, Lepper HS, Croghan TW (2000) Depression Is a Risk Factor for Noncompliance With Medical Treatment. Arch Intern Med 160:2101. doi: 10.1001/archinte.160.14.2101

116. Park H, Hong Y, Lee H, et al (2004) Individuals with type 2 diabetes and depressive symptoms

exhibited lower adherence with self-care. J Clin Epidemiol 57:978–984. doi: 10.1016/j.jclinepi.2004.01.015

117. McKellar JD, Humphreys K, Piette JD (2004) Depression Increases Diabetes Symptoms by Complicating Patients' Self-Care Adherence. Diabetes Educ 30:485–492. doi: 10.1177/014572170403000320

118. Mello A de AF de, Mello MF de, Carpenter LL, Price LH (2003) Update on stress and depression: the role of the hypothalamic-pituitary-adrenal (HPA) axis. Rev Bras Psiquiatr 25:231–238. doi: 10.1590/S1516-44462003000400010

119. Chan O, Inouye K, Riddell MC, et al (2003) Diabetes and the hypothalamo-pituitary-adrenal (HPA) axis. Minerva Endocrinol 28:87–102.

120. Pariante CM, Lightman SL (2008) The HPA axis in major depression: classical theories and new developments. Trends Neurosci 31:464–8. doi: 10.1016/j.tins.2008.06.006

121. Pariante CM (2003) Depression, stress and the adrenal axis. J Neuroendocrinol 15:811–2.

122. Burke HM, Davis MC, Otte C, Mohr DC (2005) Depression and cortisol responses to psychological stress: A meta-analysis. Psychoneuroendocrinology 30:846–856. doi: 10.1016/j.psyneuen.2005.02.010

123. Taylor MK, Reis JP, Sausen KP, et al (2008) Trait Anxiety and Salivary Cortisol During Free Living and Military Stress. Aviat Space Environ Med 79:129–135. doi: 10.3357/ASEM.2131.2008

124. Vreeburg SA, Zitman FG, van Pelt J, et al (2010) Salivary Cortisol Levels in Persons With and Without Different Anxiety Disorders. Psychosom Med 72:340–347. doi: 10.1097/PSY.0b013e3181d2f0c8

125. Felber J-P, Golay A (2002) Pathways from obesity to diabetes. Int J Obes 26:S39–S45. doi: 10.1038/sj.ijo.0802126

126. Luppino FS, de Wit LM, Bouvy PF, et al (2010) Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. Arch Gen Psychiatry 67:220–9. doi: 10.1001/archgenpsychiatry.2010.2

127. Labad J, Price JF, Strachan MWJ, et al (2010) Symptoms of depression but not anxiety are associated with central obesity and cardiovascular disease in people with type 2 diabetes: the Edinburgh Type 2 Diabetes Study. Diabetologia 53:467–71. doi: 10.1007/s00125-009-1628-9

128. Carnethon MR, Kinder LS, Fair JM, et al (2003) Symptoms of Depression as a Risk Factor for Incident Diabetes: Findings from the National Health and Nutrition Examination Epidemiologic Follow-up Study, 1971-1992. Am J Epidemiol 158:416–423. doi: 10.1093/aje/kwg172

129. Carney RM, Freedland KE, Veith RC (2005) Depression, the Autonomic Nervous System, and Coronary Heart Disease. Psychosom Med 67:S29–S33. doi: 10.1097/01.psy.0000162254.61556.d5

130. Bajkó Z, Szekeres C-C, Kovács KR, et al (2012) Anxiety, depression and autonomic nervous system dysfunction in hypertension. J Neurol Sci 317:112–116. doi: 10.1016/j.jns.2012.02.014

131. Handschin C, Spiegelman BM (2008) The role of exercise and PGC1alpha in inflammation and chronic disease. Nature 454:463–9. doi: 10.1038/nature07206

132. Raison CL, Miller AH (2011) Is Depression an Inflammatory Disorder? Curr Psychiatry Rep 13:467–475. doi: 10.1007/s11920-011-0232-0

133. Lu S, Peng H, Wang L, et al (2013) Elevated specific peripheral cytokines found in major depressive disorder patients with childhood trauma exposure: a cytokine antibody array analysis. Compr Psychiatry 54:953–61. doi: 10.1016/j.comppsych.2013.03.026

134. O'Donovan A, Hughes BM, Slavich GM, et al (2010) Clinical anxiety, cortisol and interleukin-6: evidence for specificity in emotion-biology relationships. Brain Behav Immun 24:1074–7. doi: 10.1016/j.bbi.2010.03.003

135. Serretti A, Mandelli L (2010) Antidepressants and body weight: a comprehensive review and meta-analysis. J Clin Psychiatry 71:1259–72. doi: 10.4088/JCP.09r05346blu

136. Andersohn F, Schade R, Suissa S, Garbe E (2009) Long-Term Use of Antidepressants for Depressive Disorders and the Risk of Diabetes Mellitus. Am J Psychiatry 166:591–598. doi: 10.1176/appi.ajp.2008.08071065

137. Khoza S, Barner JC, Bohman TM, et al (2012) Use of antidepressants and the risk of type 2 diabetes mellitus: a nested case–control study. Int J Clin Pharm 34:432–438. doi: 10.1007/s11096-012-9608-4

138. McIntyre RS, Soczynska JK, Konarski JZ, Kennedy SH (2006) The effect of antidepressants on glucose homeostasis and insulin sensitivity: synthesis and mechanisms. Expert Opin Drug Saf 5:157–168. doi: 10.1517/14740338.5.1.157

139. Deuschle M (2013) Effects of antidepressants on glucose metabolism and diabetes mellitus type 2 in adults. Curr Opin Psychiatry 26:60–5. doi: 10.1097/YCO.0b013e32835a4206

140. Kessler RC (2003) Epidemiology of women and depression. J Affect Disord 74:5–13.

141. Cherrington A, Wallston KA, Rothman RL (2010) Exploring the relationship between diabetes self-efficacy, depressive symptoms, and glycemic control among men and women with type 2 diabetes. J Behav Med 33:81–9. doi: 10.1007/s10865-009-9233-4

142. Lloyd CE, Dyer PH, Barnett AH (2000) Prevalence of symptoms of depression and anxiety in a diabetes clinic population. Diabet Med 17:198–202. doi: 10.1046/j.1464-5491.2000.00260.x

143. Powers SI, Laurent HK, Gunlicks-Stoessel M, et al (2016) Depression and anxiety predict sex-specific cortisol responses to interpersonal stress. Psychoneuroendocrinology 69:172–179. doi: 10.1016/j.psyneuen.2016.04.007

144. Fisher L, Mullan JT, Arean P, et al (2010) Diabetes distress but not clinical depression or depressive symptoms is associated with glycemic control in both cross-sectional and longitudinal analyses. Diabetes Care 33:23–8. doi: 10.2337/dc09-1238

145. Markowitz SM, Gonzalez JS, Wilkinson JL, Safren SA (2011) A review of treating depression in diabetes: emerging findings. Psychosomatics 52:1–18. doi: 10.1016/j.psym.2010.11.007

146. Gonzalez JS, Fisher L, Polonsky WH (2011) Depression in diabetes: have we been missing something important? Diabetes Care 34:236–9. doi: 10.2337/dc10-1970

147. Richardson LK, Egede LE, Mueller M, et al (2008) Longitudinal effects of depression on glycemic control in veterans with Type 2 diabetes. Gen Hosp Psychiatry 30:509–514. doi: 10.1016/j.genhosppsych.2008.07.001

148. de Groot M, Anderson R (2001) Association of depression and diabetes complications: a meta-analysis. Psychosom. …

149. Roy MS, Roy A, Affouf M (2007) Depression is a Risk Factor for Poor Glycemic Control and

Retinopathy in African-Americans With Type 1 Diabetes. Psychosom Med 69:537–542. doi: 10.1097/PSY.0b013e3180df84e2

150. Novak M, Mucsi I, Rhee CM, et al (2016) Increased Risk of Incident Chronic Kidney Disease, Cardiovascular Disease, and Mortality in Patients With Diabetes With Comorbid Depression. Diabetes Care 39:1940–1947. doi: 10.2337/dc16-0048

151. Ciechanowski PS, Katon WJ, Russo JE (2000) Depression and diabetes: impact of depressive symptoms on adherence, function, and costs. Arch Intern Med 160:3278–85. doi: 10.1001/ARCHINTE.160.21.3278

152. Gore M, Brandenburg NA, Dukes E, et al (2005) Pain Severity in Diabetic Peripheral Neuropathy is Associated with Patient Functioning, Symptom Levels of Anxiety and Depression, and Sleep. J Pain Symptom Manage 30:374–385. doi: 10.1016/j.jpainsymman.2005.04.009

153. Black S, Markides K, Ray L (2003) Depression predicts increased incidence of adverse health outcomes in older Mexican Americans with type 2 diabetes. Diabetes Care

154. Egede LE, Nietert PJ, Zheng D (2005) Depression and All-Cause and Coronary Heart Disease Mortality Among Adults With and Without Diabetes. Diabetes Care 28:1339–1345. doi: 10.2337/diacare.28.6.1339

155. Katon W, Rutter C, Simon G (2005) The association of comorbid depression with mortality in patients with type 2 diabetes. Diabetes …

156. Mykletun A, Bjerkeset O, Overland S, et al (2009) Levels of anxiety and depression as predictors of mortality: the HUNT study. Br J Psychiatry 195:118–25. doi: 10.1192/bjp.bp.108.054866

157. Egede LE (2004) Diabetes, Major Depression, and Functional Disability Among U.S. Adults. Diabetes Care 27:421–428. doi: 10.2337/diacare.27.2.421

158. Eren İ, Erdi Ö, Şahin M (2008) The effect of depression on quality of life of patients with type II diabetes mellitus. Depress Anxiety 25:98–106. doi: 10.1002/da.20288

159. Moussavi S, Chatterji S, Verdes E, et al (2007) Depression, chronic diseases, and decrements in health: results from the World Health Surveys. Lancet (London, England) 370:851–8. doi: 10.1016/S0140-6736(07)61415-9

160. Ciechanowski PS, Katon WJ, Russo JE (2000) Depression and Diabetes. Arch Intern Med 160:3278. doi: 10.1001/archinte.160.21.3278

161. Le TK, Able SL, Lage MJ (2006) Resource use among patients with diabetes, diabetic neuropathy, or diabetes with depression. Cost Eff Resour Alloc 4:18. doi: 10.1186/1478-7547-4-18

162. Simon GE, Katon WJ, Lin EHB, et al (2007) Cost-effectiveness of Systematic Depression Treatment Among People With Diabetes Mellitus. Arch Gen Psychiatry 64:65. doi: 10.1001/archpsyc.64.1.65

163. Katon WJ, Russo JE, Von Korff M, et al (2008) Long-term effects on medical costs of improving depression outcomes in patients with depression and diabetes. Diabetes Care 31:1155–9. doi: 10.2337/dc08-0032

164. Villamil-Salcedo V, Vargas-Terrez BE, Caraveo-Anduaga J, et al (2017) Glucose and cholesterol stabilization in patients with type 2 diabetes mellitus with depressive and anxiety symptoms by problem-solving therapy in primary care centers in Mexico City. Prim Health Care Res Dev. doi: 10.1017/S1463423617000512

165. Egede LE, Walker RJ, Payne EH, et al (2017) Effect of psychotherapy for depression via home telehealth on glycemic control in adults with type 2 diabetes: Subgroup analysis of a randomized clinical trial. J Telemed Telecare 1357633X1773041. doi: 10.1177/1357633X17730419

166. IDF Clinical Guidelines Task Force (2006) Global Guideline for Type 2 Diabetes: Recommendations for standard, comprehensive, and minimal care. Diabet Med. doi: 10.1111/j.1464-5491.2006.01918.x

167. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. (2013) Canadian Diabetes Association 2013 clinical practice guidelines for the prevention and management of diabetes in Canada. Can J Diabetes. doi: 10.1016/j.jcjd.2013.01.009

168. Egede LE, Ellis C (2010) Diabetes and depression: Global perspectives. Diabetes Res Clin Pract 87:302–312. doi: 10.1016/j.diabres.2010.01.024

169. Holt RIG, de Groot M, Golden SH (2014) Diabetes and depression. Curr Diab Rep 14:491. doi: 10.1007/s11892-014-0491-3

170. Pirraglia PA, Gupta S (2007) The interaction of depression and diabetes: a review. Curr Diabetes Rev 3:249–51.

CHAPTER 2:

DEPRESSION, ANXIETY AND RISK OF TYPE 2 DIABETES: A SYSTEMATIC REVIEW AND META-ANALYSIS OF LONGITUDINAL STUDIES

Preface

The purpose of the study presented in this chapter was to systematically summarize the available evidence for the associations betwen depression, anxiety, and concurrent depression-anxiety and Type 2 diabetes onset, and to generate pooled estimates for these effects. This study tests the first two hypotheses outlined in Chapter 1, namely: 1) that the effect of depression on diabetes onset is attenuated in studies controlling for concurrent symptoms of anxiety and vice versa, and 2) that these associations with diabetes onset are stronger in men than women.

The article presented in this chapter is formatted for submission to a scientific journal with the following author list: Naicker.K, Clayborne Z.M., Dupuis G., Øverland S., Johnson JAJ., Manuel D., & Colman I. All tables and figures are marked as primary and supplemental and follow the main text as per submission standards. Additional supporting documents related to quality assessment and reporting standards are included in appendices at the end of this chapter. Ethical approval was not required for this study.

Contribution Statement: I was responsible for formulating the study hypothesis and design, with guidance from supervisors and co-authors. I was one of the two reviewers who screened eligible articles at each stage (i.e., abstract screening and full-text review), and who performed quality assessments of the included studies. I conducted the necessary statistical analyses, generated all of the tables and figures, and drafted the final manuscript. I will also be responding to all comments arising from the peer review process.

ABSTRACT

Background/Objective: Depression and anxiety are two of the most frequently occurring psychiatric conditions in individuals with Type 2 diabetes. Evidence suggests that both depression and anxiety are associated with an increased risk of Type 2 diabetes onset, but previous meta-analyses have focused solely on depression. The primary aim of this meta-analysis was therefore to assess the risk of incident Type 2 diabetes associated with baseline 1) depression, 2) anxiety, and 3) concurrent depression-anxiety. The secondary aim was to generate pooled estimates of these effects across a range of relevant study characteristics.

Methods: An electronic search for journal articles was performed on May 1st, 2017 in two major health research databases (Ovid MEDLINE and CINAHL). Two reviewers screened all abstracts and full-text articles, and performed quality assessments using the Ottawa-Newcastle Scale. Random effects models were used to generate pooled effect estimates based on adjustment for similar baseline covariates in high quality studies. Time-to-event and point estimates were analyzed and reported separately. Funnel plots and Egger's test statistics were generated to assess publication bias.

Results: Of the 1370 articles originally screened, 47 were included in this review (38 reporting on depression, 4 on anxiety, and 1 reporting on both exposures). Publication bias was evident in the studies of depression, but not in studies of anxiety. The pooled incident diabetes risk was 1.81 (95% CI: 1.50, 2.12) for depression and 1.30 (95% CI: 1.08, 1.53) for anxiety, in studies controlling for similar baseline covariates. Diabetes risk in both cases was higher in men than women when stratified by sex. Higher effect sizes were noted in studies that controlled for antidepressant use, had shorter follow-up times (<10 years), and used clinical diagnostic interviews rather than self-report to measure depression and anxiety.

Conclusion/Interpretation: Depression and anxiety are moderately associated with diabetes onset, and these effects appear to be stronger in men and non-significant in women. Few studies of depression adjust for the co-occurring presence of anxiety, and further studies are needed that consider anxiety in the literature. No studies to date have examined the risk of diabetes onset associated with concurrent depression-anxiety, representing a gap in the current literature.

2.1 INTRODUCTION

Depression is one of the most frequently occurring psychiatric conditions in individuals with Type 2 diabetes, with a lifetime prevalence of 17.6%, roughly double that seen in the general population [1]. Rates of lifetime anxiety disorders are even higher, with as many as 19.5% of diabetic individuals affected [2]. A growing body of evidence suggests that both depression and anxiety are associated with increased risk of Type 2 diabetes onset. According to the most widely cited meta-analyses to date, depression in non-diabetic individuals is associated with a 37-60% increase in risk of Type 2 diabetes onset, independent of other major risk factors [3]. Other systematic reviews in this area have also reported significant pooled associations between depression and risk of developing the metabolic syndrome [4] and insulin resistance [5], both of which appear as precursors to diabetes. While a further meta-analysis has determined that people with diabetes are more likely to report current anxiety disorders (OR=1.20) and elevated anxiety symptoms (OR=1.48) [6], no reviews conducted to date have examined the risk of diabetes onset associated with antecedent anxiety.

A number of pathogenic mechanisms describing the relationship between depression and diabetes have been proposed, including activation of stress-mediated neuroendocrinological pathways (i.e., through the hypothalamic-pituitary-adrenal axis), followed by glucose dysregulation [7]. Depression-related eating disturbances, lethargy, or antidepressant medications may also trigger weight gain and visceral obesity, leading to insulin resistance and diabetes onset [8]. Depression may also activate proinflammatory and autoimmune responses [9], such as increases in circulating cytokine and c-reactive protein levels, which interfere with insulin signalling and can trigger insulin deficiency [10]. Anxiety disorders also have profound effects on the endocrine system, most notably by triggering ‘fight or flight’ sympathoadrenal responses [11], by disrupting sleep cycles [12], or by inducing hypertension and other

autonomic nervous system dysfunctions [13], all of which may lead to issues with glucose regulation. There is strong evidence that individuals experiencing both depression and anxiety simultaneously have a much poorer prognosis with respect to a range of mental and physical outcomes than those experiencing either disorder individually [14]. Depression and anxiety co-occur at high rates in the general population, with over 50% of individuals diagnosed with major depression in primary care settings also receiving a concurrent anxiety disorder diagnosis [14, 15]. Rates of concurrent depression-anxiety are reported as being three times higher in diabetic patients than health controls (i.e., 21.0% versus 7.3%) [16]. Given the potential negative impact of psychological comorbidities on diabetes prognoses, the co-occurrence of depression and anxiety in Type 2 diabetes is of substantial interest.

Although previous meta-analyses have attempted to estimate the risk of Type 2 diabetes associated with depression [3, 17–21], the two largest and most recent reviews failed to exclude either studies that included Type 1 diabetes [21] or cross-sectional studies[20]. These are issues that limit our ability to judge the directionality of these associations or to comment specifically on Type 2 diabetes incidence. In addition, none of the reviews undertaken to date controlled for the presence of anxiety, or reported on concurrent anxiety as a covariate of interest. The primary aim of this meta-analysis was therefore to assess the risk of incident Type 2 diabetes associated with baseline 1) depression, 2) anxiety, and 3) concurrent depression-anxiety. The secondary aim was to generate pooled estimates of these effects across a range of relevant study characteristics (e.g., participant sex, adjustment for antidepressant medication use or body mass index, type of diagnostic tool used, and study follow-up length), all of which may influence assessments of diabetes risk. We hypothesized that: 1) the effect of depression on diabetes onset would be attenuated in studies controlling for concurrent symptoms of anxiety, and vice versa, and 2) these associations with diabetes onset would be stronger in men than women.

2.2 METHODS

2.1 Literature Search

An electronic search for journal articles was performed on May 1st, 2017 in two major health research databases (Ovid MEDLINE and the Cumulative Index to Nursing and Allied Health Literature (CINAHL)). Keywords included “depression”, “depressive disorders”, “anxiety”, “anxiety disorders”, “generalized anxiety disorder”, “diabetes mellitus”, and “type 2 diabetes”, among others. The search strategies employed a set of eligibility criteria described in the following paragraph, and the detailed search strategy is provided in Supplemental Table 2.1. In addition, reference lists from relevant review papers were scanned for eligible articles. Two epidemiologists with training and experience in performing systematic reviews independently screened all abstracts returned from the search, as well as all full manuscripts that were deemed potentially relevant.

2.2 Eligibility Criteria

Studies were included in the systematic review if they met the following criteria: 1) the outcome of interest was incident Type 2 diabetes; 2) the exposure of interest was either depression, anxiety, or both; 3) the study design was longitudinal in nature (cohort, case-control, or RCT); and 4) relative measures of effect (relative risk (RR), odds ratios (OR), or hazard ratio (HR)) or the data needed to calculate them were reported. If the same dataset was used in multiple studies, the most recently published results were selected. We excluded studies that examined the use of antidepressant medication only in relation to Type 2 diabetes incidence [22–24].

2.3 Data Extraction

Data were extracted on the following study characteristics: study design, sample size, country, follow-up time, % female, mean age, diabetes assessment, exposure assessment tool, effect

estimates, and a complete list of covariates. If multiple datasets were analysed in a single study, each respective estimate was included in the meta-analyses. When multiple risk estimates were presented for different levels of depressive/anxious symptoms, those corresponding to the highest cut-off for symptom severity were used. A full list of the study characteristics extracted, including reported risk estimates and adjustment variables for included studies, are presented in Supplemental Tables 2.1 and 2.2.

2.4 Quality Assessment

All articles were given a quality score out of 9 based on the Newcastle-Ottawa scale [25]. This is a commonly used tool for assessing quality and risk of bias in observational studies, that was specifically adapted to be used with both case-control and cohort studies. Studies were considered to be sufficiently adjusted if they controlled for age, sex, and BMI at a minimum. Two reviewers independently scored each article, and inter-rater reliability was scored using Cohen's kappa. All disagreements were resolved with input from a third reviewer.

2.5 Statistical Analyses

A meta-analysis of the extracted risk estimates was performed. Odds ratios were used as an approximation for relative risk, as the incidence of the outcome was deemed to be sufficiently low (<5%) in all studies. Time-to-event (i.e., hazard ratios) and point estimates (i.e., relative risks) were analyzed and reported separately. When necessary, confidence intervals were constructed from standard errors and vice versa.

Random effects models were used to generate pooled relative risks and pooled hazard ratios. This approach is more conservative than fixed-effects models in situations where heterogeneity between studies exists [26], and was selected as the study samples in question were drawn from a wide range of different study populations. Heterogeneity of studies was quantified using Cochrane's Q test and the I-squared measure. To ensure that our pooled estimates were based

only on high quality studies, articles with a quality score below 7 were excluded from the meta-analyses. Primary pooled estimates were based on models that controlled for similar baseline covariates (i.e., age, sex, and BMI only). A secondary set of pooled estimates based on maximally adjusted models were also generated, to allow for comparisons with previous research. Publication bias was assessed by generating Begg's funnel plots and corresponding Egger's test statistics. All analyses were performed using STATA 14.0.

2.3. RESULTS

The database searches returned 1,013 articles in Ovid MEDLINE, and 815 records in CINAHL. After duplicates were removed, 1,356 unique records were retrieved from database searching. An additional 14 articles were identified from hand-searching the reference lists of related studies. Titles and abstracts for all 1,370 articles were screened by two investigators. Of these, 144 abstracts were identified for full-text review. Eighty-four articles were excluded during full-text review and 60 were included in quality assessment and data extraction. During data extraction, an additional 13 articles were excluded for various reasons (i.e., inappropriate study design or no relative effect estimate reported; Figure 2.1). Forty-seven articles were subsequently included in this review, 38 reporting on depression as an exposure, 4 reporting on anxiety, 1 article reporting estimates for both exposures, and 4 articles that did not differentiate between symptoms (which we classified as 'mixed depression-anxiety'). None of the retrieved articles reported on the concurrent effect of depression and anxiety on diabetes onset. The number of included participants was 888,111 for depression studies, 190,836 for anxiety studies, and 173,563 for mixed depression-anxiety studies. A full list of the included studies and their study characteristics is given in Supplemental Table 2.2.

All included articles were published between 1996 and 2015. Publication bias was evident in the Begg's funnel plot of risk of estimates for depression studies (Figure 2.2), as well as the Egger's test ($p<0.01$). No evidence of publication bias was present in studies of anxiety (Egger's test: $p=0.43$). The mean quality score across studies was 6.7, and 27 studies were awarded a quality score higher than 7 (i.e., 23 depression studies and 4 anxiety studies). None of the 4 studies reporting on mixed depressive and anxious symptoms received a quality score above 7 and were therefore excluded from meta-analyses. We observed a high degree of concordance between reviewers (358 out of 414 questions, Cohen's kappa=0.85). Of the included high-

quality studies, 19 depression studies and 4 anxiety studies controlled for similar baseline covariates and were included in meta-analyses.

Overall, the pooled incident diabetes risk was 1.81 (95% CI: 1.50, 2.12) for depression and 1.30 (95% CI: 1.08, 1.53) for anxiety, in studies controlling for similar baseline covariates (Figure 2.3). The corresponding risk estimates using fully adjusted estimates were 1.53 (95% CI: 1.32, 1.73) for depression, and 1.13 (95% CI: 0.98, 1.28) for anxiety. When stratified by estimate type, the pooled relative risk of Type 2 diabetes onset associated with depression was 2.03 (95% CI: 1.60, 2.46), and the hazard ratio was 1.63 (95% CI: 1.23, 2.04) (Figure 2.4). The relative risk associated with anxiety was 1.28 (95% CI: 0.75, 2.18) (this estimate was based on one study only [27]). The pooled hazard ratio associated with anxiety was 1.31 (95% CI: 1.07, 1.55). By sex, the only significant effect estimates corresponded to an increased risk of diabetes onset in men with baseline depression (RR=1.38 (95% CI: 1.17, 2.73); HR=1.82 (95% CI: 1.55, 2.10) and anxiety (RR=2.31 (95% CI:1.27, 4.19); HR=1.40 (95% CI: 1.12, 1.68)) (Table 2.1). Pooled estimates for incident diabetes in women only were not significant.

The majority of studies used self-report rather than clinical diagnostic tools to measure depression and anxiety (Table 2.1). For studies of depression, those using clinical diagnostic tools returned higher pooled estimates (RR=2.43 (95% CI:1.64, 3.22) and HR=1.77 (95% CI: 1.04, 2.50) than those using self-report. Only one study of depression reported using a clinical diagnostic tool (RR=1.28 [95% CI: 0.75, 2.18). In studies that controlled for body mass or weight, the relative risk and hazard ratio were attenuated downward in depression studies (Table 2.1). All four anxiety studies controlled for this factor. The majority of depression studies did not control for antidepressant use, but in those that did the relative risk associated with depression (RR=3.17 (95% CI: 2.08, 4.26); HR=1.68 (95% CI: 1.08, 2.62)) appeared to be higher than in those that did not (RR=1.78 and HR=1.63, respectively). No studies of depression controlled for concurrent symptoms of anxiety at baseline, and studies with shorter follow-up

times (2-10 years) yielded stronger and more significant pooled estimates than those with follow-up times greater than 10 years.

2.4. DISCUSSION

This large meta-analysis of high quality longitudinal studies found moderate increases in the relative risk of incident Type 2 diabetes associated with baseline depression and anxiety, respectively. Of the 47 included studies, 15 new studies of depression were added since the last meta-analyses was conducted on the association between depression and diabetes [20]. A pooled estimate for anxiety was also calculated based on four longitudinal studies, which to our knowledge is the first time this has been done to date. This is also the first time a meta-analysis on this topic has reported separate pooled time-to-event and point estimates over a range of relevant study characteristics. Overall, we found the retrieved literature to be dominated by studies of depression, with relatively sparse (albeit more recent) attention paid to anxiety disorders. Furthermore, we found that no studies examined diabetes risk associated with concurrently high depression and anxiety. We were therefore unable to determine whether comorbidity between these psychiatric conditions substantially increases diabetes risk beyond their individual presences. To our mind, this represents a significant gap in the current research literature.

A number of important study characteristics were highlighted in this review. While the majority of studies adjusted for sex, only six depression studies and two anxiety studies reported sex-specific risk estimates. These results revealed a more than two-fold increase in diabetes risk associated with baseline anxiety in men, as well as a similar increased risk associated with depression. Neither of the corresponding associations were significant in women, and baseline anxiety was associated with a lower diabetes risk in women, although this relationship was not significant. While mood disorders tend to be diagnosed more frequently in women [28], there is evidence that men are disproportionately more likely to develop dysglycemia in the presence of depression [29, 30], and heightened pro-inflammatory responses in the presence of anxiety

[31]. Comorbid depression and anxiety have also been shown to result in higher increases in mortality risk in men with Type 2 diabetes [32]. Conversely, anxiety is shown to have positive associations with diet adherence in women [33], and the presence of comorbid anxiety is associated with lower mortality risk in women with Type 2 diabetes [32]. While the majority of research in this area continues to adjust for rather than stratify by sex, these findings point to the potential importance of the latter approach.

Differences were also observed with respect to the type of diagnostic tool used, with higher estimates reported in studies using structured clinical interviews for depression. While the validity of self-report psychiatric instruments in epidemiological studies has received some scrutiny [34], these tools are also lauded as being more sensitive to clinically relevant subthreshold events than binary diagnostic measures [35]. Research from the Baltimore Epidemiologic Catchment Area follow-up suggests that self-report tools display a bias towards underreporting when compared with clinical psychiatric assessments, and that risk estimates using these measures tend to be conservative [34]. The present meta-analysis supports these findings, suggesting that diabetes risk may be underestimated in studies using self-report tools to measure depression. The small number of anxiety studies using clinical diagnostic tools made a corresponding comparison difficult.

A further key finding of this review is that very few of the included studies demonstrated sufficient rigor in controlling for, or differentiating between, concurrent symptoms of depression and anxiety. Of the four studies we included in the 'mixed depression-anxiety' category, two originally claimed to report specifically on the effect of depressive symptoms, but actually measured depression using a scale that included both depressive and anxious symptoms (e.g., MHI-5) [36, 37]. In addition, none of the included longitudinal studies of depression appear to have controlled for concurrent anxiety symptoms. Given the high cross-over between these disorders, it is therefore difficult to disentangle the effects of depression

from that of anxiety in these studies, despite the relatively large number of studies conducted on this topic. Studies of anxiety, on the other hand, tended to control for depression as a key covariate, making these estimates more independent in this regard.

The effect of depression on diabetes onset was attenuated downwards in studies controlling for BMI or weight, indicating a partial confounding or mediation of this relationship. BMI or obesity is one of the strongest predictors in the literature of Type 2 diabetes incidence, and is itself independently associated with depression onset [38]. Although previous research has found that depression is associated with abdominal obesity in people with diabetes, while anxiety is not [39], it is worth noting that all of the included studies of anxiety controlled for BMI. Conversely, very few studies controlled for antidepressant use, despite evidence that some of these medications can have diabetogenic effects, while others may actually reduce hyperglycemia and normalise glucose homeostasis [40]. Although our results revealed stronger estimates in studies that controlled for antidepressant use, we did not have data on the types of antidepressants used, and the number of relevant studies was low. It is therefore difficult to anticipate the overall influence of this variable on study results. Lastly, we found that studies with a longer follow-up time tended to report weaker estimates. This finding is supported by a previous review, which found that studies with 5 years or less of follow up time produced a significantly higher RR than longer studies [41]. This may be due to the proximal effects of depression or anxiety exerting indirect effects on diabetes onset through important mediational variables (e.g., obesity, diet, or hypertension), which may account for larger and larger proportions of the total effect over time. Or, conversely, cases of prediabetes or insulin resistance at baseline may be uncontrolled for in some studies and associated with depression and/or anxiety, calling into question the possibility of reverse causation in these relationships.

4.1 Limitations

Publication bias was evident in studies reporting on depression as an exposure, indicating that this pooled estimate might in fact be an artifact of bias. Other work examining publication bias indicates that it is difficult to interpret these effects in the presence of between-study heterogeneity, and that current methods of testing or adjusting for publication bias in the presence of heterogeneity are ineffective unless the meta-analyses in question is extremely large [42]. Given the presence of between-study heterogeneity in the present analyses, we therefore did not perform any adjustments on this value, and this assessment of publication bias should be interpreted with caution. It is also likely that the pooled risk estimate associated with depression is confounded by anxiety, as none of the included studies adjusted for anxiety as a covariate. Furthermore, the assessments of both depression and anxiety were performed using a wide range of measurement tools, some of which are infrequently used in research practice. These scores are also prone to vary naturally over time, as both depression and anxiety can be episodic in nature [43, 44], but the majority of the studies in question used only one measurement at baseline. The presence of unmeasured or residual confounding in studies also cannot be excluded as an explanation for the observed associations.

4.2 Strengths

Unlike previous reviews, we performed a comprehensive quality assessment of all studies and included only high-quality studies in the final meta-analyses. We excluded studies in which the time sequence of events was unclear, as well as studies that did not differentiate between Type 1 and Type 2 diabetes. Given the high degree of heterogeneity in the included study samples, we selected a conservative random effects model in our analyses. As previous reviews have found that different patterns of confounders across studies added to the heterogeneity of results

[20], we also generated our primary pooled estimates using a consistent set of confounders selected *a priori*.

4.3 Conclusions

Depression is associated with a modest increase in Type 2 diabetes risk, though we are unable to determine if these effects are independent from symptoms of anxiety. Anxiety appears to be associated with a similar increase in diabetes risk, independent from symptoms of depression. Further research is needed to determine if concurrent depression and anxiety increase diabetes risk beyond their individual estimates. Given the relative lack of studies on anxiety, further studies are needed that consider this exposure in the literature. Self-report scales for depression and anxiety may slightly underestimate diabetes risk compared to diagnostic tools in these studies. Future research should aim to better differentiate and control for co-occurring depression and anxiety at the study design stage, and endeavour to report sex-specific estimates as a standard approach.

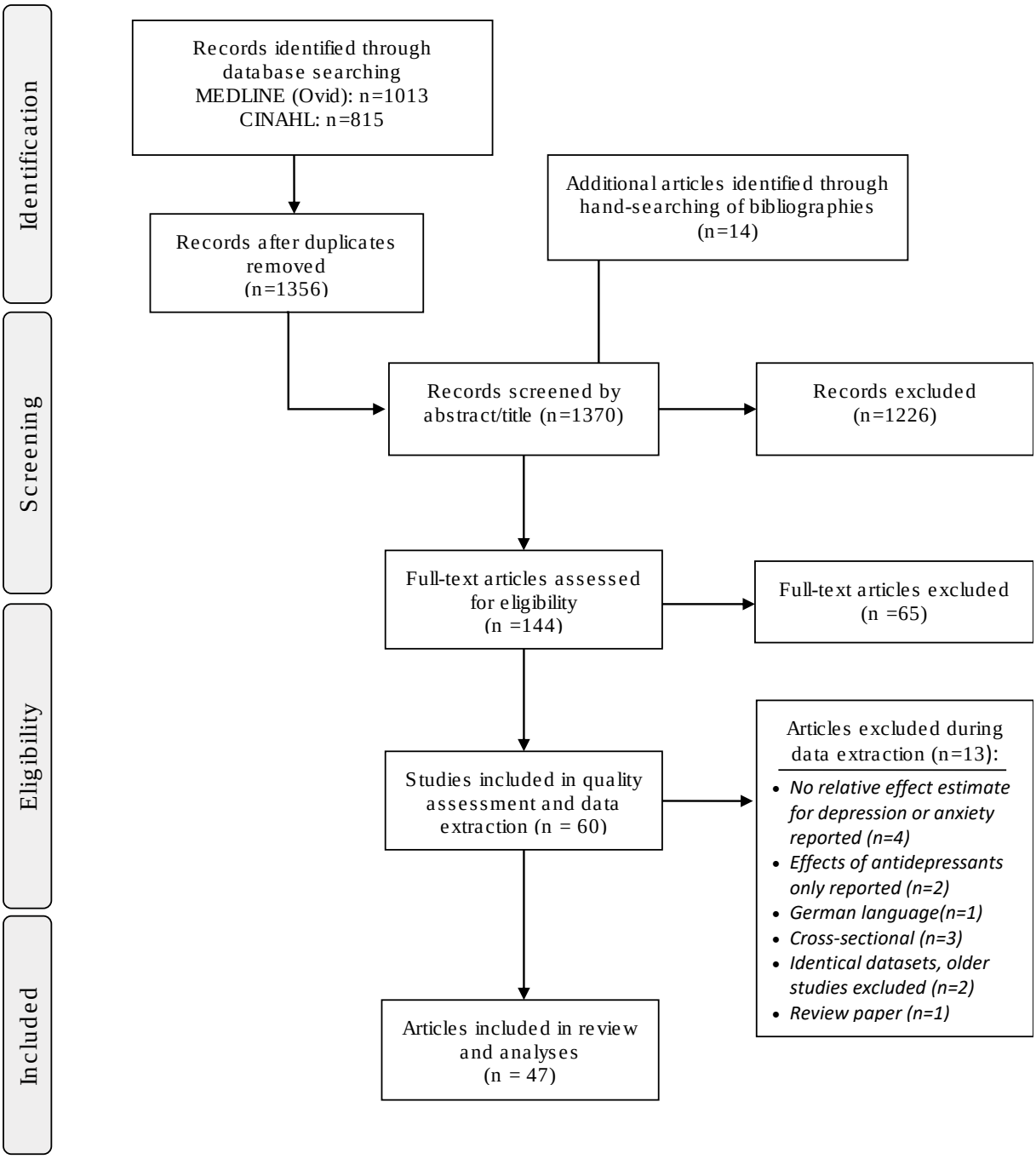
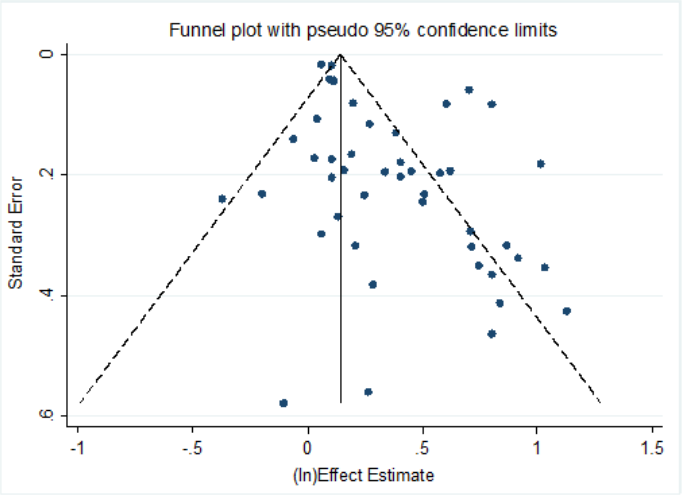
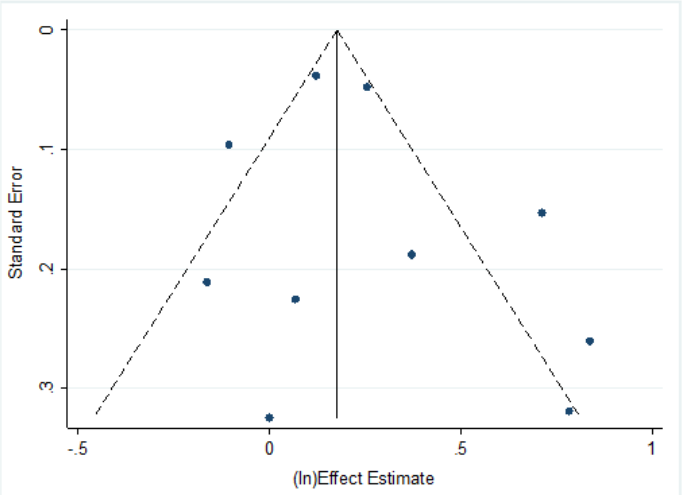


Figure 2.1. PRISMA flow diagram illustrating selection of studies for meta-analyses

a)



b)



c)

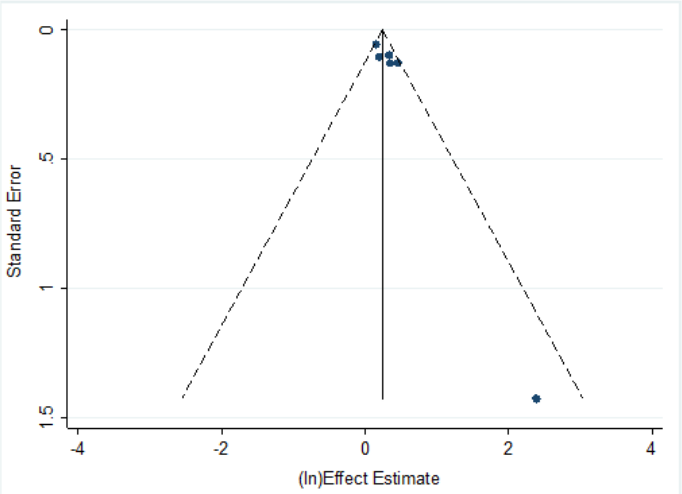


Figure 2.2. Begg's funnel plot of risk estimates for a) depression (Egger's test: p<0.01); b) anxiety (Egger's test: p=0.43); and c) mixed anxiety and depression (Egger's test: p=0.03)

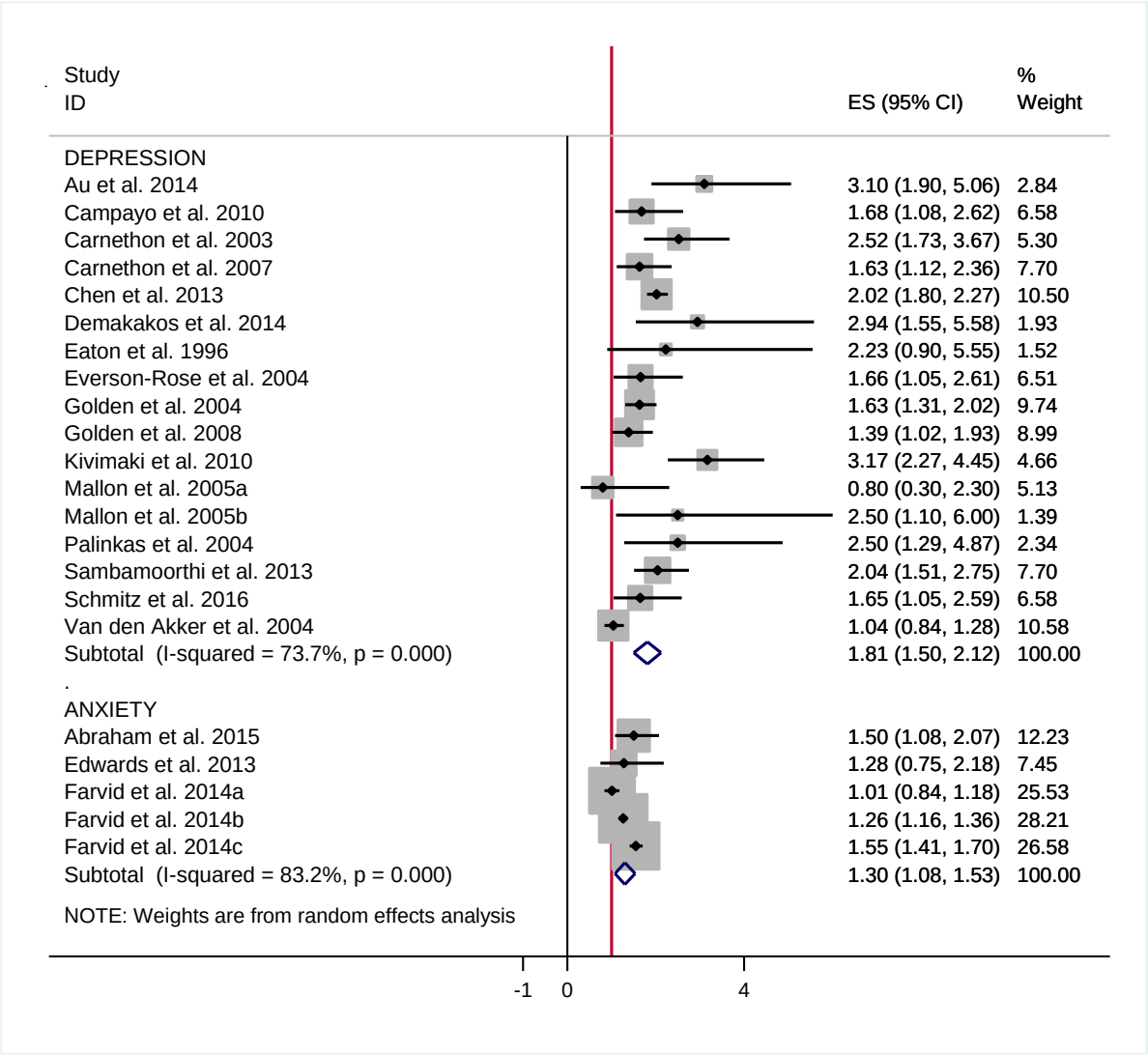


Figure 2.3. Forest plot of incident Type 2 diabetes risk associated with baseline depression and anxiety (high quality studies only, using estimates controlling for similar baseline covariates)

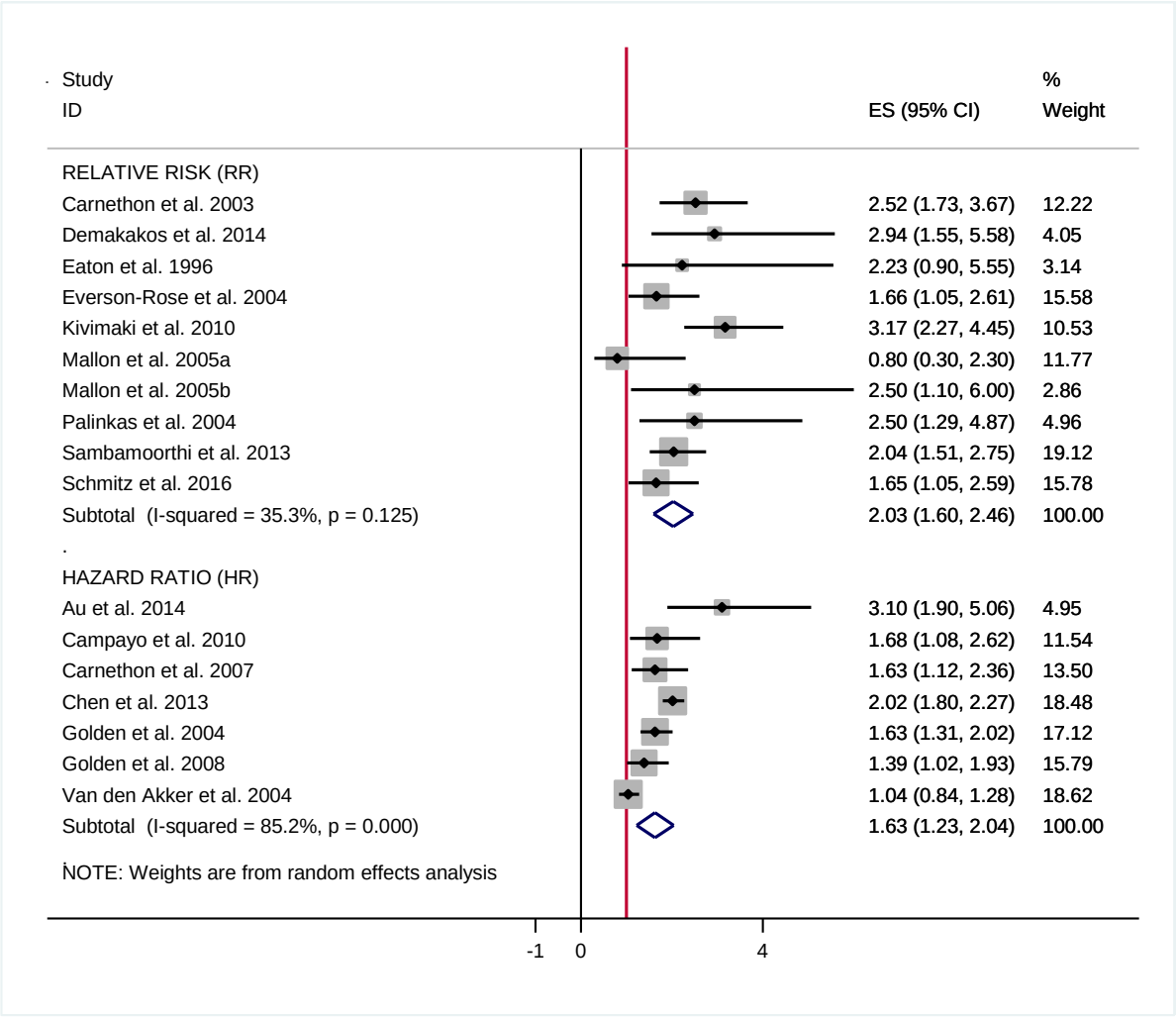


Figure 2.4. Forest plot of incident Type 2 diabetes risk associated with baseline depression, by estimate type (point estimate versus time-to-event)

Table 2.1. Pooled relative risks (RRs) and hazard ratios (HRs) for incident Type 2 diabetes associated with baseline presence of depression or anxiety, stratified by characteristics of included studies*

	Pooled RR (95% CI)				Pooled HR (95% CI)			
	(n)	Depression	(n)	Anxiety	(n)	Depression	(n)	Anxiety
Sex								
Men	**2**	1.38 (1.17, 2.73)	**1**	2.31 (1.27, 4.19)	**2**	1.82 (1.55, 2.10)	**1**	1.40 (1.12, 1.68)
Women	**3**	1.50 (0.74, 2.26)	**1**	0.85 (0.56, 1.27)	**2**	1.53 (0.14, 2.91)	**2**	1.01 (0.84, 1.18)
Diagnostic tool (exposure)								
Self-report	**9**	1.76 (1.11, 2.34)	**2**	1.40 (0.05, 2.79)	**3**	1.55 (1.30, 1.81)	**4**	1.31 (1.07, 1.55)
Clinical diagnoses/screening	**3**	2.43 (1.64, 3.22)	**1**	1.28 (0.75, 2.18)	**4**	1.77 (1.04, 2.50)	**0**	-
Control for antidepressant use								
Yes	**1**	3.17 (2.08, 4.26)	**1**	1.28 (0.75, 2.18)	**1**	1.68 (1.08, 2.62)	**1**	1.50 (1.06, 2.07)
No	**11**	1.78 (1.24, 2.33)	**2**	1.40 (0.05, 2.79)	**6**	1.63 (1.18, 2.08)	**3**	1.28 (1.01, 1.54)
Control for body mass or weight								
Yes	**9**	1.80 (1.16, 2.44)	**3**	1.20 (0.58, 1.82)	**5**	1.61 (1.35, 1.86)	**4**	1.31 (1.07, 1.55)
No	**3**	2.32 (1.21, 3.43)	**0**	-	**2**	1.53 (0.57, 2.49)	**0**	-
Control for concurrent symptoms of depression or anxiety at baseline								
Yes	**0**	-	**1**	1.28 (0.75, 2.18)	**0**	-	**1**	1.50 (1.08, 2.07)
No	**12**	1.93 (1.36, 2.50)	**2**	1.40 (0.05, 2.79)	**7**	1.63 (1.23, 2.04)	**3**	1.28 (1.01, 1.54)
Follow-up time								
2 - 10 years	**6**	2.10 (1.63, 2.57)	**1**	2.04 (1.51, 2.75)	**5**	1.77 (1.43, 2.11)	**0**	-
>10 years	**6**	1.64 (0.77, 2.50)	**2**	1.20 (0.58, 1.82)	**2**	1.26 (0.70, 1.82)	**4**	1.31 (1.07, 1.55)

* Calculated using high-quality studies only, using estimates from models controlling for similar baseline covariates (age, sex, SES and BMI)

* n = number of study datasets

Supplemental Table 2.1. Database search strategies employed for meta-analysis

Database Searched	
MEDLINE (OVID)	CINAHL
1. Depression/ 2. Depressive Disorder/ 3. Dysthymic Disorder/ 4. Depressive Disorder, Major/ 5. depress*.ti,ab. 6. dysthym*.ti,ab. 7. 1 or 2 or 3 or 4 or 5 or 6 8. Anxiety/ or Anxiety Disorders/ 9. anxiety.ti,ab. 10. anxiety disorders.ti,ab. 11. 8 or 9 or 10 12. diabetes mellitus/ or diabetes mellitus, type 2/ 13. exp cohort studies/ 14. Longitudinal.ti,ab. 15. (cohort adj (study or studies)).ti,ab. 16. (observational adj (study or studies)).ti,ab. 17. Cohort analy$.ti,ab. 18. 13 or 14 or 15 or 16 or 17 19. 7 or 11 20. 12 and 18 and 19 21. (diabetes adj3 onset).ti,ab. 22. 18 or 21 23. 12 and 19 and 22 24. (diabetes adj3 inciden*).ti,ab. 25. 18 or 24 or 21 26. 12 and 19 and 25	TI (((MH "Anxiety") OR "anxiety" OR (MH "Anxiety Disorders") OR (MH "Generalized Anxiety Disorder") OR (MH "Self-Rating Anxiety Scale")) OR ((MH "Depression") OR (MH "Self-Rating Depression Scale") OR (MH "Hamilton Rating Scale for Depression") OR (MH "Geriatric Depression Scale") OR (MH "Edinburgh Postnatal Depression Scale") OR (MH "Death Depression Scale") OR (MH "Center for Epidemiological Studies Depression Scale") OR (MH "Beck Depression Inventory, Revised Edition"))) AND TI ((MH "Diabetes Mellitus, Type 2") OR "type 2 diabetes")

Supplemental Table 2.2. Characteristics of included studies

Study	Country	N	Study Design	Follow-up (years)	Age (mean)	Diabetes Assessment	Quality Score
Studies reporting on depression							
Atlantis *et al.* 2010 [45]	Australia	1,000	Prospective cohort	10	≥65	Self-report/medication	6
Au *et al.* 2014 [46]	UK	4,955	Prospective cohort	5.3	64.8*	Self-report	7
Bai *et al.* 2013 [47]	Taiwan	2,085	Case-control, prospective	10	46.5	Medication use	5
Brown *et al.* 2005 [48]	Canada	92,497	Case-control, retrospective	3	52	ICD-9	8
Campayo *et al.* 2010 [49]	Spain	3,521	Prospective cohort	5	71.8*	Self-report	7
Carnethon *et al.* 2003 [50]	USA	6,190	Prospective cohort	15.6	48.4*	Self-report/medical record	7
Carnethon *et al.* 2007 [51]	USA	4,681	Prospective cohort	10	72.7	Medication/FG	7
Chen *et al.* 2013 [52]	Taiwan	11,694	Case-control, prospective	7	60.1	ICD-9	7
Demakakos *et al.* 2014 [53]	UK	2,914	Prospective cohort	6	61.9*	Self-report	7
Eaton *et al.* 1996 [54]	USA	3,481	Prospective cohort	13	≥18	Self-report	8
Everson-Rose *et al.* 2004 [55]	USA	2,662	Prospective cohort	3	46.4	Self-report/FG	8
Frisard *et al.* 2015 [56]	a) USA b) USA	68,169 52,326	Clinical Trial Prospective cohort	7.6 7.6	62.8* 63.6*	Self-report Self-report	6
Gangwisch *et al.* 2015 [57]	USA	10,025	Prospective cohort	8-10	25-74	Self-report/medical records	6
Golden *et al.* 2004 [58]	USA	11,615	Prospective cohort	6	56.4*	Self-report/FG/medication	7
Golden *et al.* 2008 [59]	USA	5,201	Prospective cohort	3.2	61.5*	FG/medication	8
Hasan *et al.* 2014 [60]	Australia	3,663	Prospective cohort	21	25.5	Self-report	6
Icks *et al.* 2013 [61]	Germany	3,547	Prospective cohort	5.1	58.8	Self-report/FG/medication	6
Karakus *et al.* 2011 [62]	USA	3,645	Prospective cohort	12	55.8	Self-report	7
Kawakami *et al.* 1999 [63]	Japan	2,764	Prospective cohort	8	18-53	OGTT/FG	7
Kivimaki *et al.* 2010 [64]	Finland	5085	Case-control retrospective	4.8	-	ICD-10	9
Kumari *et al.* 2004 [65]	UK	10,308	Prospective cohort	10.5	35-55	Self-report/OGTT	6
Mallon *et al.* 2005 [66]	Sweden	1,187	Prospective cohort	12	M=54.2; F=54.6*	Self-report	7
Mezuk *et al.* 2008 [67]	USA	3,481	Prospective cohort	23	47.4*	Self-report	8

Study	Country	N	Study Design	Follow-up (years)	Age	Diabetes Assessment	Quality Score
Mezuk *et al.* 2013 [68]	Sweden	336,340	Prospective cohort	7	30+	ICD-10/medication	7
Nichols *et al.* 2011 [69]	USA	58,056	Prospective cohort	5	56.8*	ICD-9 /medication/FG	9
Palinkas *et al.* 2004 [70]	USA	971	Prospective cohort	8	66.2	Self-report/medication/FG	8
Poulsen *et al.* 2014 [71]	Denmark	7,305	Prospective cohort	7	30-69	National Diabetes Register	6
Ratliff *et al.* 2015 [72]	USA	8,704	Prospective cohort	9.76	51-64	Self-report	6
Sambamoorthi *et al.* 2013 [73]	USA	10,134	Prospective cohort	3	65+	Self-report/ICD-9	7
Saydah *et al.* 2003 [74]	USA	8,870	Prospective cohort	9.0	54.8*	Self-report/hospital record	6
Schmitz *et al.* 2016 [75]	Canada	2,525	Prospective cohort	4.6	53.9	Self-report	7
Shirom *et al.* 2012 [76]	Israel	2,807	Prospective cohort	20	-	Self-report/medication/FG	5
Stellato *et al.* 2000 [77]	USA	1,096	Prospective cohort	9	53.9	Self-report or medication	6
Tsai *et al.* 2015 [78]	Taiwan	2,995	Prospective cohort	4	53+	Self-report	7
Van den Akker *et al.* 2004 [79]	Netherlands	68,004	Retrospective cohort	15.6	38.1*	Diagnosis (IHCPPC-2)	9
Vimalananda *et al.* 2014 [80]	USA	35,898	Prospective cohort	12	42.1*	Self-report	5
Wilkins *et al.* 2011 [81]	USA	26,990	Prospective cohort	2	22+	Self-report/medication	6
Studies reporting on anxiety							
Abraham *et al.* 2015 [82]	USA	5598	Prospective cohort	9.1	61.8	Self-report/OGTT	7
Edwards *et al.* 2013 [27]	USA	1,920	Prospective cohort	11	55.2*	Self-report	7
Farvid *et al.* 2014 [83]							6
1. HPFS	USA	30,791	Prospective cohort	20	54.3*	Self-report	-
2. NHS I	USA	68,904	Prospective cohort	20	54.0*	Self-report	-
3. NHS II	USA	79,960	Prospective cohort	18	38.0*	Self-report	-
Hasan *et al.* 2016 [84]	Australia	3,663	Prospective cohort	21	25.5	Self-report	6
Studies reporting on both depression and anxiety							
Arroyo *et al.* 2004 [36]	USA	72,178	Prospective cohort	4	58.8*	Self-report	5
Atlantis *et al.* 2012 [85]	Netherlands	2,981	Prospective cohort	2	42	Self-report/medication/FG	6
Demmer *et al.* 2015 [86]	USA	3,233	Prospective cohort	17	49	Self-report/medical records	8
Engum 2007 [87]	Norway	37,291	Prospective cohort	10	55.2*	Self-report/NFG	6
Pan *et al.* 2010 [37]	USA	57 880	Prospective cohort	10	62.1*	Self-report	6

* measured in non-depressed group or non-cases at baseline; FG = test for fasting glucose; OGTT = oral glucose tolerance test

Supplemental Table 2.3. Reported risk estimates and adjustment variables for included studies

Study	Exposure Assessment Tool	% Female	Risk Estimate	Adjustment for Confounders
Studies reporting on depression				
Atlantis *et al.* 2010 [45]	Psychogeriatric Assessment Scale (PAS) - D	53.3	HR: 2.38 (1.28, 4.45)	d, i, j, k
Au *et al.* 2014 [46]	CES-D	51.5*	HR: 2.03 (1.14, 3.61)	a, b, d, e,f, g, i, j, n
Bai *et al.* 2013 [47]	ICD-9	65.5	HR: 1.40 (0.96, 2.06)	a, b, e, x
Brown *et al.* 2005 [48]	Anti-depressant use + ICD-9	49	OR: 1.47 (1.14, 1.90)	a, b, x
Campayo *et al.* 2010 [49]	Geriatric Mental State Schedule	51.9*	HR: 1.65 (1.02, 2.66)	a, b, d, e, f, g, i, j, k, m, n, t
Carnethon *et al.* 2003 [50]	General Wellbeing Survey (Dep Subscale)	48.2*	RR: 2.52 (1.73, 3.67)	a, b, c
Carnethon *et al.* 2007 [51]	CES-D	59.2	HR: 1.56 (1.07, 2.28)	a, b, c, d, f, i, j, s
Chen *et al.* 2013 [52]	ICD-9	59.6	HR: 2.02 (1.80, 2.27)	a, b, n, x
Demakakos *et al.* 2014 [53]	CES-D	52.5*	OR: 2.81 (1.40, 5.62)	a, b, d, e, f, g, i, j, n
Demmer *et al.* 2015	General Wellbeing Depression Subscale	52	RR: 1.06 (0.59, 1.90)	a, b, c, e, f, i, j
Eaton *et al.* 1996 [54]	Diagnostic Interview Schedule (DIS)	62.0	RR: 2.23 (0.90, 5.55)	a, b, c, j
Everson-Rose *et al.* 2004 [55]	CES-D	100	OR: 1.66 (1.05, 2.61)	a, b, c, e, i, j, k, x
Frisard *et al.* 2015 [56]	a) WHO-OS: CES-D b) WHO-CT: CES-D	100 100	HR: 1.12 (1.03, 1.23) HR: 1.12 (1.03, 1.22)	a, c, e, g, h, i, k, m, x
Gangwisch *et al.* 2015 [57]	CES-D	-	HR: 0.94 (0.72, 1.25)	b, e
Golden *et al.* 2004 [58]	Vital Exhaustion Scale	-	HR: 1.31 (1.04, 1.64)	a, b, c, e, f, h, i, j, o, p, q, r, x
Golden *et al.* 2008 [59]	CES-D	50*	HR: 1.21 (0.87, 1.67)	a, b, c, e, f, g, h, i, j, o, p, q, r, s, x
Hasan *et al.* 2014	DSSI/sAD	100	OR: 2.23 (1.09, 4.57)	a, b, d, e, j
Icks *et al.* 2013 [61]	CES-D	52.5	OR: 1.11 (0.74, 1.65)	a, b, d, e, f, i
Karakus *et al.* 2011 [62]	CES-D	49.0	OR: 1.50 (1.01, 2.24)	a, b, c, d, e, i, j
Kawakami *et al.* 1999 [63]	Zung Self-Rating Depression Scale	0	HR: 2.31 (1.03, 5.20)	a, b, e, f, g, i, j, m, n
Kivimaki *et al.* 2010 [64]	ICD-10/psychotherapy/work disability	-	OR: 1.05 (0.55, 2.04) OR: 2.76 (1.93, 3.94)	a, b, e, k, x (no antidep)
Kumari *et al.* 2004 [65]	GHQ (depression subscale)	31	OR: 1.25 (1.00, 1.60)	a, b, e, k, x (+ antidep
Mallon *et al.* 2005 [66]	Self-report, single item	53	RR: 0.60 (0.20, 2.00) RR: 0.80 (0.30, 3.20)	a, b, d, f, g, j, n, x
Mezuk et al. 2008 [68]	Diagnostic Interview Schedule	62	HR: 2.04 (1.09, 3.81)	a, b, c, d, e, f, g, h, i, j, k
Mezuk et al. 2013 [69]	ICD-10	57.6	OR: 1.11 (1.07, 1.15)	a, b, c, e, m, n
Nichols et al. 2011 [70]	ICD-9	55.9*	RR: 1.10 (1.02, 1.20)	a, b, f, j, n, o, p, q

Study	Exposure Assessment Tool	% Female	Risk Estimate	Adjustment for Confounders
Palinkas et al. 2004 [71]	Beck Depression Inventory	57	OR: 2.50 (1.29, 4.87)	a, b, i, j, r
Poulsen et al. 2014 [72]	Major Depression Inventory (Danish)	97.5	OR: 1.14 (0.67, 1.93)	a, b, c, e, f, i, x
Ratliff et al. 2015 [73]	CES-D	59.5*	HR: 1.06 (1.02, 1.09)	a, b, c, e, f, g, i, j, k
Sambamoorthi et al. 2013 [74]	ICD-9	58.8	OR: 2.04 (1.51, 2.75)	a, b, c, e, f, i, j, n, x
Saydah et al. 2003 [75]	CES-D	58.1*	HR: 1.11 (0.79, 1.56)	a, b, c, e, i
Schmitz et al. 2016 [76]	PHQ-9	61.0*	OR: 1.28 (0.81, 2.03)	a, b, c, e, f, h, i, m
Shirom et al. 2012 [77]	PHQ-8	30	OR: 1.33 (no CI)	a, b, e, f, i, j, m, n, o
Stellato et al. 2000 [78]	CES-D	0	OR: 3.09 (1.34, 7.12)	j, n, x
Tsai et al. 2015 [79]	CES-D	46.6	OR: 1.50 (1.05, 2.12)	a, b, e, f, g, i, j, n
Van den Akker et al. 2004 [80]	ICHPPC-2	50.9*	HR: 1.04 (0.84, 1.28)	a, b, e, j
Vimalananda et al. 2014 [81]	CES-D-20	100	RR: 1.22 (1.04, 1.43)	a, e, f, g, h, i, j, m, x
Wilkins et al. 2011 [82]	ICD-9	52.0	OR: 1.23 (0.66, 2.29)	a, b, c, d, e, f, i, j, k, n, x
Studies reporting on anxiety				
Abraham *et al.* 2015 [82]	Spielberger Trait Anxiety Scale	53.6	HR: 1.45 (1.00, 2.09) RR: 1.07 (0.69, 1.67)	a, b, c, e, f, g, h, i, j, k, l, p, q, s
Demmer *et al.* 2015 [86]	General Wellbeing Anxiety Subscale	52	F: 0.85 (0.56, 1.28) M: 2.19 (1.17, 4.09)	a, b, c, e, f, i, j
Edwards *et al.* 2013 [27]	Diagnostic Interview Schedule (DIS)	60.6*	OR: 1.00 (0.53, 1.89)	a, b, c, d, e, f, g, i, j, l, x
Farvid *et al.* 2014 [83]				
1. HPFS	Crown-Crisp Index	0	HR: 0.90 (0.74, 1.08)	a, b, d, g, h, i, j
2. NHS I	Crown-Crisp Index	100	HR: 1.13 (1.05, 1.22)	a, b, d, e, g, h, i, j, x
3. NHS II	Crown-Crisp Index	100	HR: 1.29 (1.17, 1.41)	a, b, d, e, g, h, i, j, x
Hasan *et al.* 2016 [84]	Delusion Symptoms States Inventory: State of Anxiety and Depression	100	OR: 2.31 (1.39, 3.86)	a, d, e, j, l, k
Studies reporting on mixed depression and anxiety				
Arroyo *et al.* 2004 [36]	Mental Health Index (MHI-5)	100	RR: 1.22 (1.00, 1.50)	a, f, g, i, j, m, n, x
Atlantis *et al.* 2012 [85]	CIDI + IDS-30 + Beck Anxiety Inventory	67.0	OR: 10.9 (1.7, 455.6)	a, j
Engum 2007 [87]	Anxiety and Depression Index	51.0*	M: 1.42 (1.11, 1.84) F: 1.59 (1.24, 2.04)	a, b, d, e, f, i, j, n, o, p
Pan *et al.* 2010 [37]	MHI-5/antidepressant use/self-report	100	RR: 1.17 (1.05, 1.30)	a, d, f, g, h, i, j, m

a=age; b=sex; c=ethnicity/place of birth; d=marital status; e=education/income/employment; f=smoking; g=alcohol consumption or substance use; h=diet; i=physical activity; j=BMI/waist girth/overweight; k=antidepressant/antipsychotic treatment; l=mental health/depression/anxiety; m=family history of diabetes; n=chronic conditions; o=triglycerides; p=cholesterol; q=blood pressure; r=insulin; s=inflammatory markers; t=other medications (statins etc.); x=all other variables (e.g., access to medical care, health insurance, menopausal status, sleep quality).

REFERENCES

1. Ali S, Stone MA, Peters JL, et al (2006) The prevalence of co-morbid depression in adults with Type 2 diabetes: a systematic review and meta-analysis. Diabet Med 23:1165–1173. doi: 10.1111/j.1464-5491.2006.01943.x

2. Li C, Barker L, Ford ES, et al (2008) Diabetes and anxiety in US adults: findings from the 2006 Behavioral Risk Factor Surveillance System. Diabet Med 25:878–881. doi: 10.1111/j.1464-5491.2008.02477.x

3. Mezuk B, Eaton W, Albrecht S, Golden S (2008) Depression and type 2 diabetes over the lifespan a meta-analysis. Diabetes Care

4. Pan A, Keum N, Okereke OI, et al (2012) Bidirectional association between depression and metabolic syndrome: a systematic review and meta-analysis of epidemiological studies. Diabetes Care 35:1171–80. doi: 10.2337/dc11-2055

5. Kan C, Silva N, Golden SH, et al (2013) A systematic review and meta-analysis of the association between depression and insulin resistance. Diabetes Care 36:480–9. doi: 10.2337/dc12-1442

6. Smith KJ, Béland M, Clyde M, et al (2013) Association of diabetes with anxiety: A systematic review and meta-analysis. J Psychosom Res 74:89–99. doi: 10.1016/j.jpsychores.2012.11.013

7. McIntyre RS, Soczynska JK, Konarski JZ, et al (2011) Should Depressive Syndromes Be Reclassified as "Metabolic Syndrome Type II"?

8. Rustad JK, Musselman DL, Nemeroff CB (2011) The relationship of depression and diabetes: Pathophysiological and treatment implications. Psychoneuroendocrinology 36:1276–1286. doi: 10.1016/j.psyneuen.2011.03.005

9. Vaccarino V, Johnson BD, Sheps DS, et al (2007) Depression, Inflammation, and Incident Cardiovascular Disease in Women With Suspected Coronary Ischemia. J Am Coll Cardiol 50:2044–2050. doi: 10.1016/j.jacc.2007.07.069

10. Esser N, Legrand-Poels S, Piette J, et al (2014) Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. Diabetes Res Clin Pract 105:141–150. doi: 10.1016/j.diabres.2014.04.006

11. Graeff FG (2007) Anxiety, panic and the hypothalamic-pituitary-adrenal axis. Rev Bras Psiquiatr 29 Suppl 1:S3-6.

12. Bartoli AJ, Gregory AM (2017) Sleep and Anxiety. In: Wiley Handb. Dev. Psychopathol. John Wiley & Sons, Ltd, Chichester, UK, pp 215–232

13. Bajkó Z, Szekeres C-C, Kovács KR, et al (2012) Anxiety, depression and autonomic nervous system dysfunction in hypertension. J Neurol Sci 317:112–116. doi: 10.1016/j.jns.2012.02.014

14. Hirschfeld RMA (2001) The Comorbidity of Major Depression and Anxiety Disorders: Recognition and Management in Primary Care. Prim Care Companion J Clin Psychiatry 3:244–254.

15. Olfson M, Fireman B, Weissman MM, et al (1997) Mental disorders and disability among patients in a primary care group practice. Am J Psychiatry 154:1734–40. doi: 10.1176/ajp.154.12.1734

16. Rajput R, Gehlawat P, Gehlan D, et al (2016) Prevalence and predictors of depression and

anxiety in patients of diabetes mellitus in a tertiary care center. Indian J Endocrinol Metab 20:746–751. doi: 10.4103/2230-8210.192924

17. Knol MJ, Twisk JWR, Beekman ATF, et al (2006) Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. Diabetologia 49:837–845. doi: 10.1007/s00125-006-0159-x

18. Cosgrove MP, Sargeant LA, Griffin SJ (2008) Does depression increase the risk of developing type 2 diabetes? Occup Med (Chic Ill) 58:7–14. doi: 10.1093/occmed/kqm105

19. Hasan SS, Clavarino AM, Mamun AA, et al (2013) Population impact of depression either as a risk factor or consequence of type 2 diabetes in adults: A meta-analysis of longitudinal studies. Asian J Psychiatr 6:460–472. doi: 10.1016/j.ajp.2013.09.008

20. Rotella F, Mannucci E (2013) Diabetes mellitus as a risk factor for depression. A meta-analysis of longitudinal studies. Diabetes Res Clin Pract 99:98–104. doi: 10.1016/j.diabres.2012.11.022

21. Yu M, Zhang X, Lu F, Fang L (2015) Depression and Risk for Diabetes: A Meta-Analysis. Can J Diabetes 39:266–272. doi: 10.1016/j.jcjd.2014.11.006

22. Pan A, Sun Q, Okereke OI, et al (2012) Use of antidepressant medication and risk of type 2 diabetes: results from three cohorts of US adults. Diabetologia 55:63–72. doi: 10.1007/s00125-011-2268-4

23. Barnard K, Peveler RC, Holt RIG (2013) Antidepressant medication as a risk factor for type 2 diabetes and impaired glucose regulation: systematic review. Diabetes Care 36:3337–45. doi: 10.2337/dc13-0560

24. Pyykkönen A-J, Räikkönen K, Tuomi T, et al (2012) Association between depressive symptoms and metabolic syndrome is not explained by antidepressant medication: results from the PPP-Botnia Study. Ann Med 44:279–88. doi: 10.3109/07853890.2010.543921

25. Wells G, Shea B, O'Connell D, Peterson J (2012) The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analysis. Ottawa Heal. Res. Insititute Website

26. Borenstein M, Hedges L V., Higgins JPT, Rothstein HR (2010) A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods 1:97–111. doi: 10.1002/jrsm.12

27. Edwards LE, Mezuk B (2012) Anxiety and risk of type 2 diabetes: evidence from the Baltimore Epidemiologic Catchment Area Study. J Psychosom Res 73:418–23. doi: 10.1016/j.jpsychores.2012.09.018

28. Branney P, White A (2008) Big boys don't cry: depression and men. Adv Psychiatr Treat 14:256–262. doi: 10.1192/apt.bp.106.003467

29. Cherrington A, Wallston KA, Rothman RL (2010) Exploring the relationship between diabetes self-efficacy, depressive symptoms, and glycemic control among men and women with type 2 diabetes. J Behav Med 33:81–9. doi: 10.1007/s10865-009-9233-4

30. Naicker K, Øverland S, Johnson JA, et al (2017) Symptoms of anxiety and depression in type 2 diabetes: Associations with clinical diabetes measures and self-management outcomes in the Norwegian HUNT study. Psychoneuroendocrinology. doi: 10.1016/j.psyneuen.2017.07.002

31. Vogelzangs N, Beekman ATF, de Jonge P, Penninx BWJH (2013) Anxiety disorders and inflammation in a large adult cohort. Transl Psychiatry 3:e249. doi: 10.1038/tp.2013.27

32. Naicker K, Johnson JA, Skogen JC, et al (2017) Type 2 Diabetes and Comorbid Symptoms of Depression and Anxiety: Longitudinal Associations With Mortality Risk. Diabetes Care

33. Hadjistavropoulos H, Lawrence B (2007) Does anxiety about health influence eating patterns and shape-related body checking among females? Pers Individ Dif 43:319–328. doi: 10.1016/j.paid.2006.11.021

34. Eaton WW, Neufeld K, Chen L-S, et al (2000) A Comparison of Self-report and Clinical Diagnostic Interviews for Depression. Arch Gen Psychiatry 57:217. doi: 10.1001/archpsyc.57.3.217

35. Karsten J, Hartman CA, Ormel J, et al (2010) Subthreshold depression based on functional impairment better defined by symptom severity than by number of DSM-IV symptoms. J Affect Disord 123:230–237. doi: 10.1016/j.jad.2009.10.013

36. Arroyo C, Hu FB, Ryan LM, et al (2004) Depressive symptoms and risk of type 2 diabetes in women. Diabetes Care 27:129–33.

37. Pan A, Lucas M, Sun Q, et al (2010) Bidirectional association between depression and type 2 diabetes mellitus in women. Arch Intern Med 170:1884–91. doi: 10.1001/archinternmed.2010.356

38. Luppino FS, de Wit LM, Bouvy PF, et al (2010) Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. Arch Gen Psychiatry 67:220–9. doi: 10.1001/archgenpsychiatry.2010.2

39. Labad J, Price JF, Strachan MWJ, et al (2010) Symptoms of depression but not anxiety are associated with central obesity and cardiovascular disease in people with type 2 diabetes: the Edinburgh Type 2 Diabetes Study. Diabetologia 53:467–71. doi: 10.1007/s00125-009-1628-9

40. McIntyre RS, Soczynska JK, Konarski JZ, Kennedy SH (2006) The effect of antidepressants on glucose homeostasis and insulin sensitivity: synthesis and mechanisms. Expert Opin Drug Saf 5:157–168. doi: 10.1517/14740338.5.1.157

41. Hasan SS, Mamun AA, Clavarino AM, Kairuz T (2015) Incidence and Risk of Depression Associated with Diabetes in Adults: Evidence from Longitudinal Studies. Community Ment Health J 51:204–210. doi: 10.1007/s10597-014-9744-5

42. Peters JL, Sutton AJ, Jones DR, et al (2010) Assessing publication bias in meta-analyses in the presence of between-study heterogeneity. J R Stat Soc Ser A (Statistics Soc 173:575–591. doi: 10.2307/40666276

43. Angst J, Gamma A, Rössler W, et al (2009) Long-term depression versus episodic major depression: Results from the prospective Zurich study of a community sample. J Affect Disord 115:112–121. doi: 10.1016/j.jad.2008.09.023

44. Wollburg E, Roth WT, Kim S (2011) Effects of Breathing Training on Voluntary Hypo- and Hyperventilation in Patients with Panic Disorder and Episodic Anxiety. Appl Psychophysiol Biofeedback 36:81–91. doi: 10.1007/s10484-011-9150-5

45. Atlantis E, Browning C, Sims J, Kendig H (2010) Diabetes incidence associated with depression and antidepressants in the Melbourne Longitudinal Studies on Healthy Ageing (MELSHA). Int J Geriatr Psychiatry 25:688–96. doi: 10.1002/gps.2409

46. Au B, Smith KJ, Gariépy G, Schmitz N (2014) C-reactive protein, depressive symptoms, and risk of diabetes: Results from the English Longitudinal Study of Ageing (ELSA). J Psychosom Res 77:180–186. doi: 10.1016/j.jpsychores.2014.07.012

47. Bai Y-M, Su T-P, Chen M-H, et al (2013) Risk of developing diabetes mellitus and hyperlipidemia among patients with bipolar disorder, major depressive disorder, and schizophrenia: a 10-year nationwide population-based prospective cohort study. J Affect Disord 150:57–62. doi: 10.1016/j.jad.2013.02.019

48. Brown LC, Majumdar SR, Newman SC, Johnson JA (2005) History of Depression Increases Risk of Type 2 Diabetes in Younger Adults. Diabetes Care 28:

49. Campayo A, de Jonge P, Roy JF, et al (2010) Depressive Disorder and Incident Diabetes Mellitus: The Effect of Characteristics of Depression. Am J Psychiatry 167:580–588. doi: 10.1176/appi.ajp.2009.09010038

50. Carnethon MR, Kinder LS, Fair JM, et al (2003) Symptoms of Depression as a Risk Factor for Incident Diabetes: Findings from the National Health and Nutrition Examination Epidemiologic Follow-up Study, 1971-1992. Am J Epidemiol 158:416–423. doi: 10.1093/aje/kwg172

51. Carnethon MR, J C, FL B, et al (2007) Longitudinal Association Between Depressive Symptoms and Incident Type 2 Diabetes Mellitus in Older Adults. Arch Intern Med 167:802. doi: 10.1001/archinte.167.8.802

52. Chen P-C, Chan Y-T, Chen H-F, et al (2013) Population-based cohort analyses of the bidirectional relationship between type 2 diabetes and depression. Diabetes Care 36:376–82. doi: 10.2337/dc12-0473

53. Demakakos P, Zaninotto P, Nouwen A (2014) Is the association between depressive symptoms and glucose metabolism bidirectional? Evidence from the English Longitudinal Study of Ageing. Psychosom Med 76:555–61. doi: 10.1097/PSY.0000000000000082

54. Eaton WW, Armenian H, Gallo J, et al (1996) Depression and Risk for Onset of Type II Diabetes: A prospective population-based study. Diabetes Care 19:

55. Everson-Rose SA, Meyer PM, Powell LH, et al (2004) Depressive Symptoms, Insulin Resistance, and Risk of Diabetes in Women at Midlife. Diabetes Care 27:

56. Frisard C, Gu X, Whitcomb B, et al (2015) Marginal structural models for the estimation of the risk of Diabetes Mellitus in the presence of elevated depressive symptoms and antidepressant medication use in the Women's Health Initiative observational and clinical trial cohorts. BMC Endocr Disord 15:56. doi: 10.1186/s12902-015-0049-7

57. Gangwisch JE, Gross R, Malaspina D (2015) Differential Associations Between Depression, Risk Factors for Insulin Resistance and Diabetes Incidence in a Large U.S. Sample. Isr J Psychiatry Relat Sci 52:85–90.

58. Golden SH, Williams JE, Ford DE, et al (2004) Depressive Symptoms and the Risk of Type 2 Diabetes: The Atherosclerosis Risk in Communities study. Diabetes Care 27:429–435. doi: 10.2337/diacare.27.2.429

59. Golden SH, Lazo M, Carnethon M, et al (2008) Examining a bidirectional association between depressive symptoms and diabetes. Jama J Am Med Assoc 299:2751–2759.

60. Hasan SS, Clavarino AM, Dingle K, et al (2014) Psychological Health and the Risk of Diabetes Mellitus in Australian Women: A 21-Year Prospective Study. J Women's Heal 23:912–919. doi: 10.1089/jwh.2014.4832

61. Icks A, Albers B, Haastert B, et al (2013) Diabetes incidence does not differ between subjects with and without high depressive symptoms - 5-year follow-up results of the Heinz Nixdorf Recall Study. Diabet Med 30:65–69. doi: 10.1111/j.1464-5491.2012.03724.x

62. Karakus MC, Patton LC (2011) Depression and the Onset of Chronic Illness in Older Adults: A 12-Year Prospective Study. J Behav Health Serv Res 38:373–382. doi: 10.1007/s11414-011-9234-2

63. Kawakami N, Takatsuka N, Shimizu H, Ishibashi H (1999) Depressive symptoms and occurrence of type 2 diabetes among Japanese men. Diabetes Care 22:

64. Kivimaki M, Hamer M, Batty GD, et al (2010) Antidepressant Medication Use, Weight Gain, and Risk of Type 2 Diabetes: A population-based study. Diabetes Care 33:2611–2616. doi: 10.2337/dc10-1187

65. Kumari M, Head J, Marmot M (2004) Prospective Study of Social and Other Risk Factors for Incidence of Type 2 Diabetes in the Whitehall II Study. Arch Intern Med 164:1873. doi: 10.1001/archinte.164.17.1873

66. Mallon L, Broman J-E, Hetta J (2005) High incidence of diabetes in men with sleep complaints or short sleep duration: a 12-year follow-up study of a middle-aged population. Diabetes Care 28:2762–7.

67. Mezuk B, Eaton WW, Golden SH, Ding Y (2008) The influence of educational attainment on depression and risk of type 2 diabetes. Am J Public Health 98:1480–5. doi: 10.2105/AJPH.2007.126441

68. Mezuk B, Chaikiat Å, Li X, et al (2013) Depression, neighborhood deprivation and risk of type 2 diabetes. Health Place 23:63–9. doi: 10.1016/j.healthplace.2013.05.004

69. Nichols GA, Moler EJ (2011) Cardiovascular disease, heart failure, chronic kidney disease and depression independently increase the risk of incident diabetes. Diabetologia 54:523–526. doi: 10.1007/s00125-010-1965-8

70. Palinkas LA, Lee PP, Barrett-Connor E (2004) A prospective study of Type 2 diabetes and depressive symptoms in the elderly: The Rancho Bernardo Study. Diabet Med 21:1185–1191. doi: 10.1111/j.1464-5491.2004.01315.x

71. Poulsen K, Cleal B, Clausen T, Andersen LL (2014) Work, Diabetes and Obesity: A Seven Year Follow-Up Study among Danish Health Care Workers. PLoS One 9:e103425. doi: 10.1371/journal.pone.0103425

72. Ratliff S, Mezuk B (2015) Depressive symptoms, psychiatric medication use, and risk of type 2 diabetes: results from the Health and Retirement Study. Gen Hosp Psychiatry 37:420–6. doi: 10.1016/j.genhosppsych.2015.05.008

73. Sambamoorthi U, Ma Y, Findley PA, Rust G (2013) Antidepressant use, depression, and new-onset diabetes among elderly Medicare beneficiaries. J Diabetes 5:327–335. doi: 10.1111/1753-0407.12014

74. Saydah SH, Brancati FL, Golden SH, et al (2003) Depressive symptoms and the risk of type 2 diabetes mellitus in a US sample. Diabetes Metab Res Rev 19:202–208. doi: 10.1002/dmrr.353

75. Schmitz N, Deschênes SS, Burns RJ, et al (2016) Depression and risk of type 2 diabetes: the potential role of metabolic factors. Mol Psychiatry 21:1726–1732. doi: 10.1038/mp.2016.7

76. Shirom A, Toker S, Melamed S, et al (2012) Life and Job Satisfaction as Predictors of the Incidence of Diabetes. Appl Psychol Heal Well-Being 4:31–48. doi: 10.1111/j.1758-0854.2011.01054.x

77. Stellato RK, Feldman HA, Hamdy O, et al (2000) Testosterone, sex hormone-binding globulin, and the development of type 2 diabetes in middle-aged men: prospective results from the

Massachusetts male aging study. Diabetes Care 23:490–4.

78. Tsai AC, Lee S-H (2015) Determinants of new-onset diabetes in older adults–Results of a national cohort study. Clin Nutr 34:937–942. doi: 10.1016/j.clnu.2014.09.021

79. van den Akker M, Schuurman A, Metsemakers J, Buntinx F (2004) Is depression related to subsequent diabetes mellitus? Acta Psychiatr Scand 110:178–183. doi: 10.1111/j.1600-0447.2004.00333.x

80. Vimalananda VG, Palmer JR, Gerlovin H, et al (2014) Depressive Symptoms, Antidepressant Use, and the Incidence of Diabetes in the Black Women's Health Study. Diabetes Care 37:2211–2217. doi: 10.2337/dc13-2642

81. Wilkins TL, Sambamoorthi U (2011) Antidepressant use, depression, lifestyle factors, and new-onset diabetes. Int Clin Psychopharmacol 26:159–168. doi: 10.1097/YIC.0b013e328342ce31

82. Abraham S, Shah NG, Diez Roux A, et al (2015) Trait anger but not anxiety predicts incident type 2 diabetes: The Multi-Ethnic Study of Atherosclerosis (MESA). Psychoneuroendocrinology 60:105–13. doi: 10.1016/j.psyneuen.2015.06.007

83. Farvid MS, Qi L, Hu FB, et al (2014) Phobic anxiety symptom scores and incidence of type 2 diabetes in US men and women. Brain Behav Immun 36:176–182. doi: 10.1016/j.bbi.2013.10.025

84. Hasan SS, Clavarino AM, Mamun AA, Kairuz T (2016) Anxiety symptoms and the risk of diabetes mellitus in Australian women: evidence from 21-year follow-up. Public Health 130:21–28. doi: 10.1016/j.puhe.2015.07.022

85. Atlantis E, Vogelzangs N, Cashman K, Penninx BJWH (2012) Common mental disorders associated with 2-year diabetes incidence: The Netherlands Study of Depression and Anxiety (NESDA). J Affect Disord 142:S30–S35. doi: 10.1016/S0165-0327(12)70006-X

86. Demmer RT, Gelb S, Suglia SF, et al (2015) Sex differences in the association between depression, anxiety, and type 2 diabetes mellitus. Psychosom Med 77:467–77. doi: 10.1097/PSY.0000000000000169

87. Engum A (2007) The role of depression and anxiety in onset of diabetes in a large population-based study. J Psychosom Res 62:31–38. doi: 10.1016/j.jpsychores.2006.07.009

Appendix 2A. Quality assessment of included articles in systematic review using the Ottawa-Newcastle Scale

Article	Q1			Q2			Q3			Q4			Q5			Q6			Q7			Q8			Q9		
	R1	R2	All	R1	R2	All	R1	R2	All	R1	R2	All	R1	R2	All	R1	R2	All	R1	R2	All	R1	R2	All	R1	R2	All
Abraham *et al.* 2015	*	*	*	*	*	*	-	-	-	*	*	*	*	*	*	*	*	*	-	*	*	*	*	*	-	-	-
Arroyo *et al.* 2004	-	-	-	*	*	*	-	-	-	*	*	*	*	*	*	*	*	*	-	-	-	*	*	*	-	-	-
Atlantis *et al.* 2010	*	*	*	*	*	*	*	-	-	*	*	*	-	*	*	*	*	*	-	-	-	*	*	*	-	-	-
Atlantis *et al.* 2012	-	-	-	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	-	-	-	*	*	*	*	*	*
Au *et al.* 2014	*	*	*	*	*	*	-	-	-	*	*	*	*	*	*	*	*	*	-	-	-	*	*	*	*	-	*
Bai *et al.* 2013	-	*	-	*	*	*	*	*	-	-	*	*	-	-	-	*	*	*	-	*	*	*	*	*	-	-	-
Brown *et al.* 2005	-	*	*	*	*	*	*	*	*	*	*	*	-	-	-	*	*	*	*	*	*	*	*	*	-	*	*
Campayo *et al.* 2010	*	*	*	*	*	*	-	*	*	*	*	*	*	*	*	*	*	*	-	-	-	*	*	*	-	-	-
Carnethon *et al.* 2003	*	*	*	*	*	*	-	-	-	*	*	*	*	*	*	*	*	*	-	*	-	*	*	*	*	-	*
Carnethon *et al.* 2007	*	*	*	*	*	*	-	-	-	*	*	*	*	*	*	*	*	*	-	-	-	*	*	*	*	*	*
Chen *et al.* 2013	-	*	*	*	*	*	*	*	*	*	*	*	-	-	-	*	*	*	*	*	*	*	*	*	-	-	-
Demakakos *et al.* 2014	*	*	*	*	*	*	-	-	-	*	*	*	*	*	*	*	*	*	-	-	-	*	*	*	*	-	*
Demmer *et al.* 2015	*	*	*	*	*	*	-	*	-	*	*	*	*	*	*	*	*	*	-	*	*	*	*	*	*	-	*
Eaton *et al.* 1996	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	-	-	-	*	*	*	-	*	*
Edwards *et al.* 2013	*	*	*	*	*	*	*	*	*	*	*	*	*	-	*	*	*	*	-	*	-	*	*	*	-	-	-
Engum 2007	*	*	*	*	*	*	-	-	-	*	*	*	*	*	*	*	*	*	-	-	-	*	*	*	-	-	-
Everson-Rose *et al.* 2004	*	*	*	*	*	*	-	-	-	*	*	*	*	*	*	*	*	*	-	*	*	*	*	*	*	*	*
Farvid *et al.* 2014	-	-	-	*	*	*	-	-	-	*	*	*	*	*	*	*	*	*	-	*	-	*	*	*	-	-	-
Frisard *et al.* 2015	*	*	*	*	*	*	-	-	-	*	*	*	*	*	*	*	*	*	-	-	-	*	*	*	-	-	-
Gangwisch *et al.* 2015	*	*	*	*	*	*	-	-	-	*	*	*	*	-	-	*	*	*	-	-	-	*	*	*	*	*	*
Golden *et al.* 2004	*	*	*	*	*	*	-	-	-	*	*	*	*	*	*	*	*	*	-	*	*	*	*	*	-	-	-
Golden *et al.* 2008	*	*	*	*	*	*	-	-	-	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	-	*
Hasan *et al.* 2014	*	-	-	*	*	*	-	-	-	*	*	*	*	*	*	*	*	*	-	-	-	*	*	*	*	*	*
Hasan *et al.* 2015	*	-	-	*	*	*	-	-	-	*	*	*	*	*	*	*	*	*	-	-	-	*	*	*	*	*	*
Icks *et al.* 2013	*	*	*	*	*	*	-	-	-	*	*	*	-	-	-	*	*	*	-	-	-	*	*	*	*	*	*
Karakus *et al.* 2011	-	*	*	*	*	*	-	-	-	*	*	*	*	*	*	*	*	*	-	-	-	*	*	*	*	*	*
Kawakami *et al.* 1999	-	-	-	*	*	*	-	-	-	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Kivimaki *et al.* 2010	-	*	*	-	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	-	*

Article	Q1			Q2			Q3			Q4			Q5			Q6			Q7			Q8			Q9		
	R1	R2	All	R2	All	All	R1	R2	All	R1	R2	All	R1	R2	All	R1	R2	All	R1	R2	All	R1	R2	All	R1	R2	All
Kumari *et al.* 2004	-	*	*	*	*	*	-	-	-	*	*	*	*	*	*	*	*	*	-	*	-	*	*	*	-	-	-
Mallon *et al.* 2005	*	*	*	*	*	*	-	-	-	*	-	*	*	*	*	*	*	*	-	-	-	*	*	*	*	*	*
Mezuk *et al.* 2008	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	-	-	-	*	*	*	*	*	*
Mezuk *et al.* 2013	*	*	*	*	*	*	*	*	*	*	*	*	-	-	-	*	*	*	*	*	*	-	*	*	*	-	-
Nichols *et al.* 2011	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	-	*
Palinkas *et al.* 2004	-	*	*	*	*	*	-	-	-	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	-	*
Pan *et al.* 2010	-	-	-	*	*	*	-	-	-	*	*	*	*	*	*	*	*	*	-	-	-	*	*	*	*	*	*
Poulson *et al.* 2014	-	*	-	*	*	*	-	-	-	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	-	-
Ratliff *et al.* 2015	*	*	*	*	*	*	-	-	-	*	*	*	*	*	*	*	*	*	-	-	-	*	*	*	*	-	-
Sambamoorthi *et al.* 2013	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	-	*	-	*	*	*	*	-	-
Saydah *et al.* 2003	*	*	*	*	*	*	-	-	-	*	*	*	*	*	*	*	*	*	-	-	-	*	*	*	-	-	-
Schmitz *et al.* 2016	-	*	*	*	*	*	-	-	-	*	*	*	*	*	*	*	*	*	-	-	-	*	*	*	*	-	*
Shirom *et al.* 2012	-	*	-	*	*	*	-	-	-	*	*	*	*	*	*	*	*	*	-	*	-	-	-	-	*	*	*
Stellato *et al.* 2000	-	*	*	*	*	*	-	-	-	*	*	*	*	*	*	*	*	*	-	-	-	*	*	*	-	-	-
Tsai *et al.* 2014	*	*	*	*	*	*	-	-	-	*	*	*	*	*	*	*	*	*	-	-	-	*	*	*	*	-	*
Van den Akker *et al.* 2004	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	-	*
Vimalananda *et al.* 2004	-	*	-	*	*	*	-	-	-	*	*	*	*	*	*	*	*	*	-	-	-	*	*	*	-	-	-
Wilkins *et al.* 2011	*	*	*	*	*	*	*	*	*	*	*	*	*	-	*	*	*	*	-	-	-	-	*	-	-	-	-

Appendix 2B. Calculation of Cohen's kappa

	Reviewer 2		
Reviewer 1	**Yes**	**No**	**Total**
Yes	278	22	300
No	34	80	114
Total	312	102	414

$\kappa = (P_o - P_{e)} / 1 - P_e$

where P_o = the relative observed agreement among raters
P_e = the hypothetical probability of chance agreement

P_o = number in agreement/total = (278 + 80)/414 = **0.86**

Chance of random "yes" agreement: R1 = 300/414 = 0.72
R2 = 312/414 = 0.75
Total = 0.72 * 0.75 = **0.54**

Chance of random "no" agreement: R1 = 114/414 = 0.28
R2 = 102/414 = 0.25
Total = 0.28 * 0.25 = **0.07**

P_e = 0.54 x 0.07 = **0.04**

κ = $(P_o - P_e) / 1 - P_e$ = (0.86 – 0.04) / 1 – 0.04 = 0.82/0.96 = **0.85**

Appendix 2C. MOOSE Checklist for meta-analyses

	Reported on page	Comments
Reporting of background should include		
Problem definition	44-45	
Hypothesis statement	45	
Description of study outcome(s)	46	
Type of exposure or intervention used	46	
Type of study designs used	46	
Study population	46	
Reporting of search strategy should include		
Qualifications of searchers (e.g. librarians and investigators)	46	
Search strategy, including time period used in the synthesis and key words	46, 62	Supplemental Table 2.1
Effort to include all available studies, including contact with authors	46	
Databases and registries searched	46	
Search software used, name and version, including special features used (e.g. explosion)	46	
Use of hand searching (e.g. reference lists of obtained articles)	46	
List of citations located and those excluded, including justification	57	
Method of addressing articles published in languages other than English	57	
Method of handling abstracts and unpublished studies	-	None found
Description of any contact with authors	-	None needed
Reporting of methods should include		
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	46-47	
Rationale for the selection and coding of data (e.g. sound clinical principles or convenience)	46-47	

Documentation of how data were classified and coded (e.g. multiple raters, blinding and interrater reliability)	46-47	
Assessment of confounding (e.g. comparability of cases and controls in studies where appropriate)	46-47	
Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	47	
Assessment of heterogeneity	47	
Description of statistical methods (e.g. complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	47-48	
Provision of appropriate tables and graphics	57-66	
Reporting of results should include		
Graphic summarizing individual study estimates and overall estimate	59-60	
Table giving descriptive information for each study included	63-66	Supplemental Tables 2-3
Results of sensitivity testing (e.g. subgroup analysis)	61	
Indication of statistical uncertainty of findings	58-60	
Reporting of discussion should include		
Quantitative assessment of bias (e.g. publication bias)	58	
Justification for exclusion	46	
Assessment of quality of included studies	63-64, 73-75	Supplemental Table 2.2 Appendix 2A, 2B
Reporting of conclusions should include		
Consideration of alternative explanations for observed results	55	
Generalization of the conclusions (i.e. appropriate for the data presented and within the domain of the literature review)	52-56	
Guidelines for future research	56	
Disclosure of funding source	-	

From: Stroup DF, Berlin JA, Morton SC, et al (2000) Meta-analysis of observational studies in epidemiology: A proposal for reporting. JAMA 283:2008–2012. doi:10.1001/jama.283.15.2008.

CHAPTER 3:

GENERAL METHODS: DESCRIPTION OF DATA SOURCE AND METHODOGICAL APPROACHES

This chapter describes the methodological elements common to the three following studies (Chapters 4-6). These elements include: a description of the data source and participants involved in each study; a description of how the exposures and outcomes were defined; general approaches to statistical analyses (including treatment of missing data and model building); and ethical approval and consent. Analytic approaches and documentation specific to each study are described within each chapter and their respective appendices. As each thesis study was written as a stand-alone manuscript for publication, the methods detailed here will often be repeated in the subsequent chapters.

3.1 Data Source and Participants

The primary data source for this thesis was the Norwegian Nord-Trøndelag Health Study, also known as the HUNT Study. The HUNT study is a large, population-based survey of residents in a restricted geographic area made up of 24 municipalities, known as Nord-Trøndelag, in central Norway. The population of Nord-Trøndelag county is highly stable, with a reported net out-migration of 0.3% per year, and fairly homogenous (over 97% Caucasian) [1]. Nord-Trøndelag is similar to the rest of Norway with respect to geography, economy, industry, age distribution, morbidity, and mortality [1]. The HUNT study was primarily set up to collect detailed health-related data on the general population, and to address four high-priority health issues: arterial hypertension, diabetes, tuberculosis screening, and quality of life [2]. The survey was conducted

in three waves, beginning in 1984-86, with the most recent wave occurring in 2006-08. All inhabitants of the county (roughly 90,000 people) aged ≥20 years were invited to participate. The questionnaires included items on demographic characteristics, health status, lifestyle and health habits, living conditions, and mental health. Clinical examinations and physical tests were also performed during each wave. Starting in HUNT 2, blood samples were also collected and analyzed. The HUNT Study now includes a state-of-the art biobank for the storage and biochemical analysis of a variety of biological samples, including blood, serum, plasma, urine, and buccal swabs for DNA analyses and genotyping [3]. The HUNT Study biobank and databanks are administered by the Norwegian University of Science and Technology (NTNU) in Levanger, Norway.

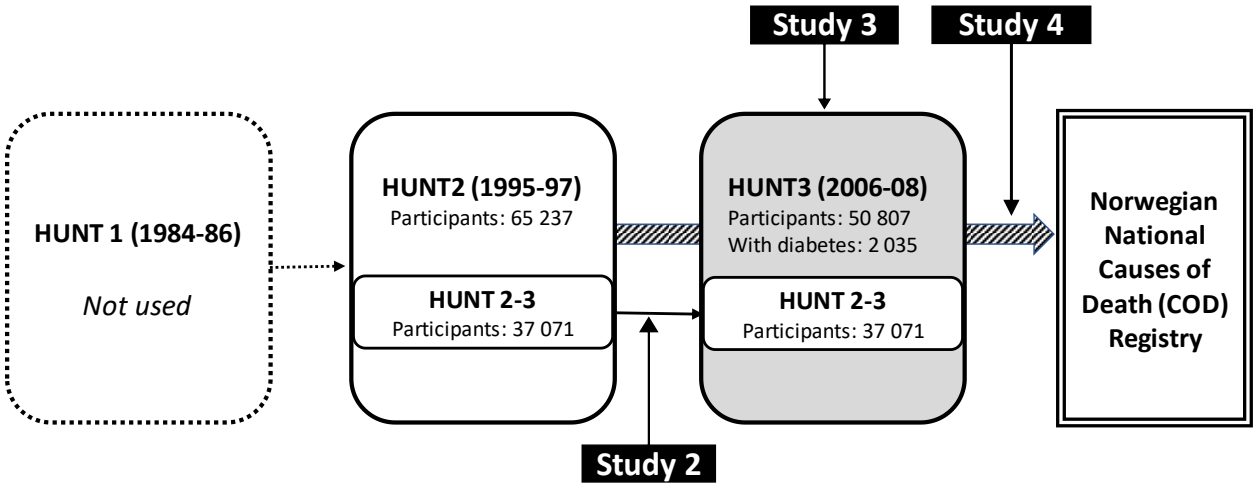


Figure 3.1 Diagram of HUNT Study cohorts used in each thesis study[1]

[1] Adapted from Figure 2 in Krokstad, S., et al. "Cohort profile: the HUNT study, Norway." *International journal of epidemiology* 42.4 (2012): 968-977.

As illustrated in Figure 3.1, each of the studies in Chapters 4-6 used a different study sample or cohort, described on the following page. HUNT 1 did not include measurements of mental health symptoms consistent with the more recent survey waves, so it was not used in the current studies.

HUNT 2-3 Cohort (*Chapter 4):* This longitudinal cohort consists of 37,071 individuals who were followed up from the second wave of the HUNT Study in 1995-97 to the third wave in 2006-08. This included 72% of women and 69% of men from HUNT 2 who participated in HUNT 3. The sample from this study included only individuals who were diabetes-free at baseline (regardless of diabetes type), and who had information on diabetes status in HUNT 3, resulting in a total study sample of 36,161 individuals.

HUNT-3 *(Chapter 5):* This represented the third wave of the HUNT study conducted in 2006-2008. Of the 93,860 residents invited, 50,807 completed the initial HUNT 3 questionnaire. Of these individuals, 2,255 were invited to participate in a detailed diabetes sub-study and questionnaire. This included a clinical confirmation of diabetes and clinical measurements (e.g., blood pressure, heart rate, BMI, etc.) and serum blood work (e.g., HBa1C levels, fasting glucose, total and HDL cholesterol, triglycerides, etc.). The final sample for the study in chapter 5 consisted of a cross-sectional sample of 2,035 individuals with Type 2 diabetes.

HUNT 2 with linkage to National Causes of Death Registry *(Chapter 6)*: This longitudinal cohort consisted of individuals followed from the second wave of the HUNT Study in 1995-1997 through to 2013. Of the 93,898 individuals invited to participate in this wave, 65,237 individuals responded. This study included individuals both with and without diagnosed Type 2 diabetes at baseline, but excluded other types of diabetes (Type 1, gestational, or latent autoimmune diabetes of adults (LADA)). The final cohort consisted of 64 177 individuals.

These study participants were then linked through their Norwegian citizen personal identity number to the Norwegian Causes of Death Registry Norway in order to assess all-cause mortality. This registry is maintained by the Norwegian Institute of Public Health, and endeavours to cover all deaths occurring in Norway (regardless of whether the deceased were registered Norwegian residents or not), as well as the deaths of all Norwegians who die abroad.

3.2 Exposure Classification

The most recent two waves of the HUNT study (HUNT 2 and HUNT 3) included an assessment of mental health symptoms known as the CONOR Mental Health Index (CONOR-MHI). The CONOR-MHI is not a clinical assessment of depression or anxiety, but is a modified version of the General Health Questionnaire (GHQ-9) and the Hopkins Symptom Checklist (HSCL-10), which were primarily designed to provide an overall measure of psychological distress. It has been evaluated against the HSCL-10 and Hospital Anxiety and Depression Scales (HADS) within both the HUNT Study and Oslo Health Study cohorts, and found to have strong accuracy when tested against each of these scales (AUC=0.902 and AUC=0.909, respectively) [4]. The internal consistency of the CONOR-MHI was also high (Cronbach alpha $\geq$0.80) across other large Norwegian datasets [4]. Like many mental health scales, the majority of items relate to either anxiety or depression. Specifically, individuals were asked: “In the last two weeks, have you felt...?” with respect to the following items (translated from the original Norwegian): ‘Calm and confident’; ‘Nervous and restless’; ‘Troubled by anxiety’; ‘Happy and optimistic’; ‘Irritable’; ‘Down or depressed’; and ‘Lonely’. The response set of each item consisted of four options: 1) “No”, 2) “A little”, 3) “A good amount”, and 4) “Very much”.

In order to verify the loadings of these items onto distinct anxiety and depression factors, with the aim of further examining associations between symptoms relating to depression and anxiety in our sample, we performed a confirmatory factor analysis on the CONOR-MHI. One-factor and two-factor models were compared. The best-fitting model consisted of a two-factor structure with distinct anxiety and depression dimensions, and excluded the optimism item (Figure 3.2).

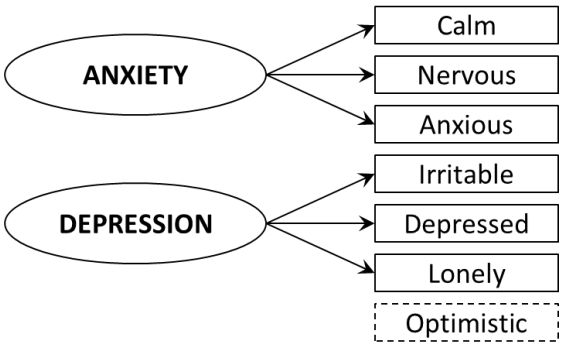


Figure 3.2: Best fitting structure of the CONOR-MHI - 2-factor structure (excludes optimism item)

The Chi-squared, comparative fit index (CFI), Tucker Lewis index (TLI), and root mean square error of approximation (RMSEA) statistics were calculated to determine model fit. These values were interpreted using the following cut-offs: for the RMSEA, values less than 0.6 are suggested to indicate good model fit, with values between 0.06 to 0.10 indicating mediocre fit and above 0.10 indicating poor fit [5, 6]. For the CFI, values ≥0.95 to 0.97 indicate good model fit [5, 6]. Similarly, for the TLI (also known as the Non-Normed Fit Index (NNFI)) values ≥0.95 to 0.97 indicate good model fit [5, 6]. The fit indices were quite strong for the above two-factor structure, as given in Table 3.1. It is worth noting that, although the p-values for the chi-square statistic were significant, the chi-square as an index of fit for factor analyses is affected by a number of issues (most notably sample size) [6]. The chi-square value increases with increasing sample size, and

large sample models are often unfairly rejected even with very small discrepancies between implied and obtained covariance matrices, and models using small samples may be too likely to be accepted (i.e., a Type II error) [5]. It is therefore recommended that a significant chi-square value should be disregarded if both the sample size exceeds 200, and other fit indices indicate that the model is acceptable. In our study, the sample sizes exceeded this and all other fit indices indicated a very good model fit.

Table 3.1: Fit statistics for factor solutions for the CONOR-MHI* (N=58,360)

	X^2 (df)	P-value	CFI	TLI	RMSEA (90%CI)
One factor	27300.724 (14)	<0.0001	0.930	0.895	0.201 [0.199-0.203]
One factor, excluding item #2	2932.142 (9)	<0.0001	0.985	0.974	0.082 [0.079-0.084]
Two factor	28173.934 (13)	<0.0001	0.928	0.883	0.211 [0.209-0.214]
Two factor, excluding item #2	773.681 (8)	<0.0001	0.996	0.992	0.044 [0.042-0.047]

*Using weighted least squares means and variance adjusted estimator (WLSMV)

3.3 Diagnosis of Type 2 diabetes

Type 2 diabetes status was determined in two stages in the HUNT Study. First, by response to a self-report item on the general questionnaire coupled with a test of non-fasting glucose levels. This was followed by a more detailed clinical and laboratory confirmation of diabetes type in all individuals who flagged as having diabetes in the first round. Type 2 diabetes was classified as those individuals who had were anti-glutamic acid decarboxylase (anti-GAD) and anti-insulinoma-associated (anti-IA-2) negative, to exclude latent autoimmune diabetes in adults (LADA) cases,

and confirmed as having not begun insulin treatment within one year of their diabetes diagnosis to exclude Type 1 cases.

As the focus of this thesis was Type 2 diabetes (and all cases of Type 1 diabetes and other types were excluded from analyses), we will frequently refer to Type 2 diabetes simply as 'diabetes' throughout the manuscript for brevity. It is also worth noting that this thesis is an exploration of the multi-morbidity between depression, anxiety, and Type 2 diabetes; as such, all of these disorders may be comorbid with one another at various points in the subsequent studies. In order to minimize confusion, as was done throughout the introduction, we will use the term 'comorbid' to refer to the co-occurrence of diabetes with either depression or anxiety, and the term 'concurrent' to refer to the co-occurrence of depression and anxiety with one another.

3.4 Statistical Analysis

3.4.1 Missing Data

While the amount of missing data for most of the HUNT Study variables of interest was fairly low (i.e., 1% to 7%), some exceptions on key variables within each study wave were noted (Table 3.2). Complete-case analyses is often the simplest and most widely used approach to handling missing data in epidemiological studies; however, there is evidence that complete case analysis often requires strong assumptions and can produce biased parameter estimates [7]. To mitigate the effect of loss of information and bias introduced by missing data in the HUNT Study, we used a multiple imputation approach for each study in chapters 4-6, as outlined below. Whereas single imputation can results in estimated standard errors that are too small, multiple imputation has been demonstrated to result in correctly estimated standard errors and confidence intervals [7]. In addition, while single imputation is only valid with small amounts of missing values, multiple

imputation is theoretically sound for larger percentages of missing values (i.e., less than 50%), especially when the amount of missing data on auxiliary variables is low.

Table 3.2 Percentage of missing data on key thesis covariates in the HUNT Study

Variable	% Missing	
	HUNT 2	HUNT 3
Age	0.00	0.00
Sex	0.00	0.00
Smoking	2.20	2.83
Education*	5.33	-
Chronic Conditions	7.03	0.02
Family history	28.51	4.62
Alcohol consumption	35.42	39.88
Physical activity	30.32	37.74
Type 2 diabetes status	1.63	1.32
Clinical measures		
Waist girth	1.64	0.88
BMI	1.2	0.79
Fasting glucose	0.71	2.89
Serum triglycerides	0.66	1.48
Systolic BP	0.78	0.65
HDL cholesterol	0.70	2.89
CONOR-MHI Items		
Depressed	11.72	6.03
Lonely	10.78	5.76
Irritable	11.70	6.56
Nervous or restless	11.32	6.32
Anxious	11.85	6.10
Calm	10.96	6.61

*Not measured in HUNT 3

For the majority of the variables listed in this table, the percentage of missing values in the HUNT 2 dataset ranged from 0.7% to 5.3%. The mental health index items were slightly higher with 10.7% to 11.70% missing. For family history of diabetes, alcohol, and physical activity, the percentage missing was higher (28% to 35%). For the HUNT 3 cohort, these ranges decreased for the mental health items (5.7% to 6.6%) and increased slightly for alcohol consumption and physical activity (39.8% and 37.7%).

Prior to imputation, patterns of missingness among the variables were examined. In the HUNT dataset, all variables appeared to be missing at random (MAR), and as such multiple imputation by chained equations (MICE) was chosen as an appropriate and flexible technique for handling the missing data. This technique was used to create 30 imputed datasets, from which pooled estimates for each variable were computed. Research shows that multiple imputation is often unbiased with missing not-at-random (NMAR) data, even when data is assumed to be MAR [8]. In order to create an imputation model that was more general than the analysis model and allowed for all possible interactions between predictor variables, a range of auxiliary variables and all associated interaction terms were included. We have included a sensitivity analyses in the appendix of each study comparing imputed and non-imputed (i.e., complete case analyses) values for the main regression models. Overall, we found very minor differences between the imputed and non-imputed results, which did not impact our study findings or their interpretation.

3.4.2 Model Building

All of the outcomes of interest in Chapters 4-6 were binary in nature, and used either logistic regression or proportional hazards modelling to generate relative measures of effect. These models included all key variables identified in our literature review and available in the dataset, in both continuous and dichotomous forms. In the latter case, each variable was first checked for outliers and subsequently dichotomized. Continuous variables, such as age, were included using cubic splines as per Harrell's method [9]. This was done to allow for the inclusion of non-linear relationships in our model (e.g., between mortality and age), and to avoid the pitfalls regularly associated with categorization of continuous variables [10].

For each statistical model, relationships between covariates and the study outcome were first explored in univariate analysis. Statistical models were then built using backwards selection, in which all possible covariates were initially included in the models. Variables with the largest p-values ($p>0.10$) were eliminated one at a time until only those significant at this level were retained. Multicollinearity was assessed by determining the variance inflation factors (VIF) for all variables in the adjusted models. All analyses were performed using STATA 14.0.

3.5 Participant Consent and Ethical Approval

Residents of Nord-Trøndelag were invited to participate in the HUNT surveys by mail, using invitation rosters created from monthly updated national census data. The invitation package included the invitation letter, an information pamphlet, a consent form, and the first questionnaire. The information pamphlets for HUNT 2 and HUNT 3 were elaborated in co-operation with the Data Inspectorate of Norway, the Health Directorate and the Regional Committee for Medical and Health Research Ethics. Participants delivered the signed consent forms and completed questionnaires at the health facilities upon their first clinical examination. All participants were apprised of the study purpose and potential harms and benefits, and provided full written consent prior to study particpation.

The collected data and samples were then stored centrally in a de-identified format with strict data access rules. The subset of data provided for this project was securely housed and accessed a host office within the Norwegian Institute of Public Health in Bergen, Norway. It was transferred to this location as a locked/encrypted file, and a building pass or escort were required to enter or exit the offices where the dataset was located.

Only research groups affiliated with a Norwegian Research Institute can apply for access to HUNT data. Projects must be approved by The Regional Committee for Medical Research in Norway (REK) and be registered with The Norwegian Social Science Data Services (NSD). This project is approved by the REK to be completed by 2019, and no subset of data provided for this project will be retained after this period. The REK approval letter is provided in Appendix A1. In addition, each published manuscript using HUNT data must be vetted and approved prior to publication. These individual letters of approval are provided at the end of each study chapter. Ethical approval was also obtained from the University of Ottawa Health Sciences and Science Research Ethics Board. A copy of this letter is provided in Appendix A1.

REFERENCES

1. Holmen J, Midthjell K, Krüger Ø, et al (2003) The Nord-Trøndelag Health Study 1995-97 (HUNT 2): Objectives, contents, methods and participation. Nor Epidemiol 13:19–32.
2. Krokstad S, Langhammer A, Hveem K, et al (2013) Cohort Profile: the HUNT Study, Norway. Int J Epidemiol 42:968–77. doi: 10.1093/ije/dys095
3. Hveem K (2011) Creation of a New Prospective Research Biobank: The Example of HUNT3. Humana Press, Totowa, NJ, pp 231–239
4. Søgaard A, Bjelland I, Tell G, Røysamb E (2003) A comparison of the CONOR Mental Health Index to the HSCL-10 and HADS. Nor. Epidemiol.
5. Hooper D, Coughlan J, Mullen M (2008) Structural Equation Modelling: Guidelines for Determining Model Fit. Electron J Bus Res Methods 6:53–60.
6. Schermelleh-Engel K, Moosbrugger H (2003) Evaluating the Fit of Structural Equation Models: Tests of Significance and Descriptive Goodness-of-Fit Measures. Methods Psychol Res Online 8:23–74.
7. Donders ART, van der Heijden GJMG, Stijnen T, Moons KGM (2006) Review: A gentle introduction to imputation of missing values. J Clin Epidemiol 59:1087–1091. doi: 10.1016/j.jclinepi.2006.01.014
8. Schafer JL, Graham JW (2002) Missing data: our view of the state of the art. Psychol Methods 7:147–77.
9. Harrell FE (2001) General Aspects of Fitting Regression Models. pp 11–40
10. Bennette C, Vickers A (2012) Against quantiles: categorization of continuous variables in epidemiologic research, and its discontents. BMC Med Res Methodol 12:21. doi: 10.1186/1471-2288-12-21

CHAPTER 4:

POPULATION ATTRIBUTABLE FRACTIONS FOR TYPE 2 DIABETES: AN EXAMINATION OF MULTIPLE RISK FACTORS INCLUDING SYMPTOMS OF DEPRESSION AND ANXIETY

Preface

The purpose of the study presented in this chapter was to was to examine the risk of diabetes onset associated with clusters of risk factors, including symptoms of depression, anxiety, and concurrent depression-anxiety, by calculating their respective population attributable fractions (PAFs). The main study hypotheses were: 1) that symptoms of depression and anxiety would each amplify the risk associated with traditional risk factors, and 2) that their effects on diabetes onset would be stronger in men than in women.

The article presented in this chapter was submitted to *Diabetes Care* on September 1, 2017 (see Appendix 4C for confirmation letter), with the following author list: Naicker, K., Manuel, D., Øverland, S., Skogen, J., Johnson, J., Sivertsen, B., & Colman, I. All tables and figures are marked as primary and supplementary corresponding to the submitted version. Additional supporting documents, including sensitivity analyses and ethical approval, are included in appendices at the end of this chapter.

Contribution Statement: I was responsible for generating the study hypothesis and design, with guidance from supervisors and co-authors. I conducted the necessary statistical analysis, created all of the tables and figures, and drafted the final manuscript. I will also be responding to all comments arising from the peer review process.

ABSTRACT

Background/Objective: Population attributable fractions (PAFs) are frequently used to quantify the proportion of Type 2 diabetes cases due to single risk factors, an approach which may result in an overestimation of their individual contributions. This study aimed to examine Type 2 diabetes incidence associated with multiple risk factor combinations, including the metabolic syndrome, behavioural factors, and symptoms of depression and anxiety.

Research Design and Methods: Using data from the population-based HUNT cohort, we examined incident diabetes in 36,161 Norwegian adults from 1995 to 2008. Attributable fractions were calculated using Miettinen's case-based formula, using relative risks estimated from multivariate regression models.

Results: Overall, the studied risk factors accounted for 50.5% of new diabetes cases (78.2% in men and 47.0% in women). Individuals exposed to both behavioural and metabolic factors were at highest risk of diabetes onset (PAF=22.9%). Baseline symptoms of anxiety and depression contributed a further 13.6% of new cases to this combination. Important differences were noted by sex, and the risk of diabetes onset was highest in men experiencing all four factors.

Conclusion/Interpretation: While traditional risk factors confer the highest risk for diabetes onset, symptoms of depression and anxiety have a significant potential to amplify the risk associated with these factors. Men appear to be particularly vulnerable to the interaction between metabolic, behavioural and psychological risk factors. This study highlights the importance of risk factor clustering in diabetes onset, and is the first that we know of to quantify the excess fraction of incident diabetes associated with psychological risk factor interactions.

4.1 INTRODUCTION

Over 400 million adults worldwide are currently diagnosed with Type 2 diabetes, a prevalence that has more than doubled over the past three decades and continues to rise [1]. To address what is increasingly referred to as a global health crisis, many countries are investing in programs aimed at reducing the main modifiable risk factors of diabetes: obesity, smoking, unhealthy eating, and physical inactivity. Alongside these traditional risk factors, psychological factors are increasingly noted as being important to the pathogenesis of diabetes [2]. It has long been suggested that the risk of Type 2 diabetes is elevated by depression [3], and a growing evidence base has established depression as an independent risk factor for diabetes onset. This body of research extends to the effects of depression on obesity [4], physical activity [5], insulin resistance [6], and glycemic control [7]. Anxiety disorders represent a less frequently studied risk factor for diabetes onset, but anxiety is shown to elicit similar effects on the dysregulation of metabolic and inflammatory processes as depression (e.g., through HPA-axis activation [8] or cytokine-mediated autoimmune responses [9]). Notably, anxiety disorders and depression are seen to occur together in over 50% of primary care cases [10].

In 2008, Cosgrove *et al.* estimated the attributable risk of developing Type 2 diabetes following an episode of depression to be 20%, and the total population fraction of diabetes cases attributable to depression at 4% [11]. Population attributable fractions (PAFs) are a common and useful method of quantifying the burden of disease attributable to a specific risk factor, and take into account both the strength of the association between the risk factor and disease and the wider population health impact of that risk factor [12]. PAFs have been used to describe the proportion of Type 2 diabetes cases due to physical inactivity [12], obesity [13], sugar intake [14], metabolic factors [15], and specific genetic variants [16]. For example, a recent study concluded that the proportion of diabetes cases attributable to sugar-sweetened beverages was

8.7% (3.9% to 12.9%) in the United States [14]. The authors concluded that, under an assumption of causality, these beverages are expected to cause approximately 2 million excess diabetes cases over 10 years in the US [14].

Although researchers are often compelled to quantify the PAFs for individual factors, the reality is that risk factors often cluster and may interact to amplify the risk associated with any one factor. Various studies have documented that individuals with certain combinations of risk factors are at higher risk of cardiovascular disease [17, 18], and that screening can be more efficient if multiple risk factors are considered [19]. As the bulk of chronic diseases and subsequent mortality are attributable to risk factor combinations, the calculation of the PAF for any risk factor individually may greatly overestimate the risk associated with that factor [20]. A relatively sparse body of research has used a multiple risk factor approach to quantify the burden of diabetes onset [21], and no studies to date appear to have included an examination of depression and anxiety. The purpose of this study was to determine the PAF for multiple risk factor combinations for Type 2 diabetes, including symptoms of depression and anxiety, in a population-based sample of Norwegian adults.

4.2 METHODS

4.2.1 Data source and participants

This study used cohort data from The Norwegian Nord-Trøndelag Health Study (HUNT Study), a population-based survey conducted over 3 waves: HUNT 1 (1984-86), HUNT 2 (1995-97) and HUNT 3 (2006-08). The HUNT study was initially established to address four major health outcomes (i.e., diabetes, hypertension, tuberculosis, and quality of life). The scope has broadened over time to include prevalence and incidence of disease, health determinants, and a state-of-the-art biobank [22]. Every citizen of Nord-Trøndelag county aged 20+ years was invited to participate. A total of 77,212 (89.4%) of those invited participated in the first wave of the survey, followed by 65,237 (69.5%) in HUNT 2, and 50 807 in HUNT 3 (54.1%) [22]. Further details of the HUNT cohort profile and methodology are well-described elsewhere [22].

The longitudinal HUNT 2-3 cohort consisted of 37,071 individuals who participated in the two most recent waves of the study. Our study sample consisted of participants in this cohort who did not have a confirmed diagnosis of diabetes (Type 1, Type 2, or LADA) at baseline in 1995-97 (HUNT 2), totaling 36,161 individuals. All participants provided written informed consent, and study protocols were approved by Norway's Regional Committee for Medical and Health Research Ethics (2014/2160/REK West).

4.2.2 Primary outcome: Type 2 diabetes onset

Our primary outcome was new Type 2 diabetes cases occurring between 1995 and 2008. Diabetes incidence was assessed in 2006-08 (HUNT 3), and confirmed based on results of three repeated laboratory tests (fasting plasma glucose, oral glucose tolerance, and serum HbA1c levels). All individuals were additionally confirmed to be anti-glutamic acid decarboxylase and anti-insulinoma-associated negative (to exclude LADA cases).

4.2.3 Risk factors for Type 2 diabetes onset

Our primary study risk factors were divided into three categories: metabolic, behavioural, and psychological. We classified the metabolic syndrome according to the International Diabetes Federation consensus worldwide definition [23]. Central obesity was indicated if waist circumference exceeded 94 cm for men or 79 cm for women. Low high-density lipoprotein (HDL) cholesterol was indicated at levels below 40 mg/dL (1.03 mmol/L) in men and 50 mg/dL (1.29 mmol/L) in women. Hypertension was indicated at a systolic blood pressure >130 mm Hg or diastolic >85 mm Hg. Random plasma glucose ≥200 mg/dL (11.1 mmol/L) was used to indicate hyperglycemia (as fasting glucose measurements were not available). The metabolic syndrome was defined as having central obesity plus any two of the latter four factors [23].

Two major behavioural factors in the onset of diabetes were included: physical inactivity and smoking. Individuals were classified as physically inactive if they fell below the cut-off of 150 minutes of moderate or 60 minutes of vigorous physical activity per week (corresponding to World Health Organization guidelines [24]). Smoking was included if either former or current daily smoking were reported, as both have known associations with diabetes onset [25], and included as total number of packyears smoked (calculations based on 20 cigarettes/pack). The presence of either of these two factors were considered an indicator of behavioural risk in calculations of population attributable fractions.

Symptoms of depression and anxiety were measured using a 7-item mental health index (CONOR-MHI). These items consisted of widely validated items from the General Health Questionnaire and the Hopkins Symptom Checklist (HSCL). The index was evaluated against both the HSCL-10 and the Hospital Anxiety and Depression Scale (HADS) within both the HUNT Study and Oslo Health Study cohorts, and found to have strong accuracy when tested against each of these scales as a gold standard (AUC=0.902 and AUC=0.909, respectively)

[26]. Individuals were classified as having depression or anxiety if their mean scores on depression or anxiety items fell above the recommended cut-off of 2.15 [26].

4.2.4 Additional covariates

Age was considered as a continuous covariate and specified using restricted cubic splines in multivariate regression analyses, to account for the non-linear relationship between age and diabetes onset (as per Harrell's method [27]). Education was classified as having completed any post-secondary versus no higher education. The presence of any additional chronic conditions (i.e., asthma, angina pectoris, any type of cancer or thyroid disease) was included dichotomously.

4.2.5 Statistical analysis

Relative risks were estimated using univariate and multivariate regression models. Analyses were performed using generalized linear mixed models for binary data in STATA 14.0. All models controlled for age and were stratified by sex. Adjusted models were constructed using all covariates and all possible two-way interaction terms. Models were built using backwards selection, and all variables significant at the α=0.10 level were included in the final models. Regressions were conducted following imputation of missing covariate values, under the multiple imputation by chained equations (MICE) method [28]. This technique created 30 imputed datasets, from which reported estimates were computed. The amount of data missing was low (1% - 7%) on almost all covariates.

The population attributable fraction (PAF) was then calculated for strata in which the relative risk was greater than 1.0 and significant at the α=0.05 level. PAFs were calculated using Miettinen's case-based formula $\mathbf{PAR_i=(RR_i-1)/RR_i \times CF_i}$, where RR_i equals the relative risk associated with the strata in question and CF_i denotes the case fraction (CF=number of exposed

cases/total number of cases) [29]. This approach was selected over the original formula for calculating attributable fractions popularized by Levin [30], as it produces internally valid estimates in the presence of confounding and when adjusted relative risks must be used. A sensitivity analysis comparing the two approaches was also conducted (see Supplemental Table 4.5).

4.3 RESULTS

Of the 36,161 participants, 55% were female and the majority were between 20-61 years of age (Table 4.1). Men and women differed to some extent with respect to all baseline diabetes risk factors, with the most pronounced differences corresponding to higher rates of central obesity and physical inactivity in women, and higher rates of hypertension and elevated triglycerides in men (Table 4.1). Overall, symptoms of either depression or anxiety were present in 8.8% of individuals at baseline. A total of 1,324 incident cases of diabetes were reported during the study period, 655 cases occurring in women and 669 cases in men.

In univariate analysis, the relative risk of diabetes incidence increased more than five-fold in the presence of the metabolic syndrome (Supplemental Table 4.1). Smoking was associated with diabetes incidence in men only (RR=1.63 [95% CI: 1.33, 2.00]), as were symptoms of depression and comorbid depression-anxiety (RR=1.65 [95% CI: 1.24, 2.20], and RR=2.07 [95% CI: 1.41, 3.05], respectively). Physical inactivity was associated with a 1.5-fold increase in diabetes risk for both sexes. Symptoms of anxiety alone were not associated with elevated diabetes risk in either sex. A dose-response increase in diabetes risk was also observed, with respect to the number of metabolic, behavioural and mental health risk factors present. This ranged from two factors (RR=2.62 [95% CI: 1.97, 3.50]) to ≥4 factors (RR=11.89 [95% CI: 9.22, 15.34]).

The final multivariate model included education and age as covariates, and excluded the presence of other chronic conditions (Supplemental Table 4.2). The presence of the metabolic syndrome alone contributed 8.4% of cases (Figure 4.1; Table 4.2). Behavioural factors alone were not associated with any new cases; however, behavioural factors in conjunction with the metabolic syndrome were associated with 22.9% of cases. In conjunction with concurrent depression-anxiety, behavioural factors contributed an additional 1.4% of cases. The strata

associated with the most incident diabetes cases was therefore the metabolic syndrome in conjunction with behavioural factors (PAF=22.9%). The presence of either depression, anxiety or concurrent depression-anxiety conferred an additional 13.6% of cases to this risk factor combination (PAFs= 2.5%, 4.9%, and 6.2%, respectively). No diabetes cases in the overall sample were attributable to the presence of psychological risk factors alone (Table 4.2).

The highest adjusted relative risk of incident diabetes was observed in individuals with all four risk factors (RR=7.47 [95% CI: 5.79, 9.64]), but this combination occurred in less than 2% of exposed individuals, resulting in a PAF of 6.2% overall. In men experiencing all four risk factors, the relative risk of diabetes was 12.57 (95% CI: 8.67, 16.22) and the PAF was 8.4% (Supplemental Table 4.4; Figure 4.1). These were substantially higher than the results observed in women (RR=4.49 [95% CI: 3.06, 6.60], PAF=4.0%) (Supplemental Table 4.3; Figure 4.2).

As illustrated in Figure 4.2, the pattern of risk for diabetes incidence was more pronounced in men than in women. Behavioural factors alone conferred a substantial proportion of cases in men only (PAF=8.9%). This proportion was even higher in the presence of symptoms of depression (PAF=10.9%). Conversely, a larger proportion of cases were attributable to the metabolic syndrome alone in women than men (PAFs= 9.8% and 6.7%, respectively). The total PAF for all risk factor combinations was 50.5% (women=47.0%, men=78.2%). In all instances, the Miettinen PAF estimates were more conservative than those calculated using Levin's formula (Supplemental Table 4.5).

4.4 DISCUSSION

This study examined the population attributable fraction of Type 2 diabetes incidence associated with the metabolic syndrome, behavioural factors, and symptoms of depression and anxiety in a cohort of Norwegian adults. Overall, these factors accounted for 50.5% of new diabetes cases, a proportion that was higher in men (78.2%) than women (47.0%). Symptoms of depression and anxiety contributed to diabetes incidence, but they did so only in conjunction with metabolic and behavioural risk factors. The group at highest risk for diabetes incidence was individuals exposed to both behavioural and metabolic factors (PAF=22.9%); symptoms of anxiety and depression contributed a further 13.6% of new cases to this combination. Men appeared to be particularly vulnerable to the interaction between metabolic, behavioural and psychological risk factors.

In the overall cohort, the PAFs associated with symptoms of depression or anxiety alone were negligible, despite our multivariate analysis reflecting a relative risk of diabetes onset of roughly 1.40 for depression, which is in line with previous research [31]. However, as mentioned above, symptoms of depression and anxiety in combination with behavioural and/or metabolic factors contributed to a substantial proportion of excess cases - a total of 19.2% across strata. For all strata containing depressive symptoms the PAF was 12.5%, considerably exceeding the 4.0% for depression alone estimated by Cosgrove *et al.* based on a risk estimate of 1.25 [11]. It is worth noting that the latter PAF was calculated using Levin's formula and examined depression risk independently, both of which could overestimate the independent PAF associated with depression when compared to our calculations. Our findings suggest that the joint effect of these factors may be more relevant to diabetes onset than their independent effects, and underscore the potential influence of psychological factors on both metabolic and behavioural processes. While many relevant mediating relationships have been documented

with respect to depression and diabetes risk factors [4–6], symptoms of anxiety appeared to have a larger impact on these relationships in our study (primarily due to the higher prevalence of anxiety in the population). Further studies in this area should examine interactions with traditional risk factors when attempting to model diabetes risk associated with depression or anxiety, as this may provide a truer depiction of their associated risk than is available in the current literature.

With respect to the metabolic syndrome, a combined fraction of 49.1% of new diabetes cases was observed across all strata containing this factor. This is in line with previous research demonstrating a metabolic syndrome PAF of 30-52% for diabetes across multiple studies [15]. The independent effect of the metabolic syndrome alone conferred a higher proportion of cases in women (9.8%) than men (6.7%). This is somewhat unexpected given that men had higher frequencies of all metabolic risk factors at baseline, with the exception of central obesity, and may point to the increased tendency of men with the metabolic syndrome to experience behavioural and psychological comorbidities than women. This finding may be partly explained by the higher prevalence of central obesity in women (47.9% versus 36.9% in men), and is in line with previous research demonstrating that central obesity is a stronger predictor of metabolic syndrome status in women than men [32]. These findings suggest that women who do not have any concurrent behavioural or psychological risk may still be particularly vulnerable to the negative consequences of metabolic risk factors such as central obesity.

Conversely, smoking and physical inactivity alone did not independently confer diabetes risk in women in our study, yet accounted for 8.9% of incident cases in men. In conjunction with symptoms of depression or anxiety, these factors were associated with another 15.0% of incident cases in men. One partial explanation for this sex-related difference may be the higher prevalence of former smoking reported by men, as well as the total number of packyears. The relationship between smoking and diabetes incidence is particularly pernicious in men, with

research reflecting that men require double the length of time following smoking cessation to return to non-smoking diabetes risk levels (≥10 years, as opposed to ≥ 5 years in women) [33].

As illustrated in Figure 2, the interaction of metabolic, behavioural, and psychological factors had a more profound impact on diabetes incidence in men than women. The relative risk was 12.5 times higher in men experiencing all four factors, accounting for 8.4% of new diabetes cases. By comparison, this risk was one third the size in women and accounted for only 4.0% of new cases. Previous research has demonstrated stronger effects of depression on glycemic control in men only [34], as well as the presence of elevated inflammation in men but not women with anxiety disorders [35]. Recent research also demonstrates higher mortality rates in men with Type 2 diabetes experiencing concurrent depression and anxiety than women [36]. It may be possible that men experiencing all four equivalent risk factors are more susceptible to their effects than women, or alternately that men reporting depression and anxiety at baseline tend to have a more severe metabolic or behavioural risk profile than women reporting these symptoms within the same strata. Future research should attempt to unpack these interactions within this high-risk group.

4.4.2 Strengths and limitations

This study used a large population-based sample of Norwegian adults, and allowed for an appropriate follow-up time to assess diabetes incidence. We rigorously controlled for a range of clinical and sociodemographic covariates and exposures. We also used a formula for calculating population attributable risk that was valid in the presence of confounding and interaction, and provided an intuitive presentation of these results. Instead of focusing on the potential proportion of diabetes cases that could be reduced by eliminating depression or anxiety in the population overall, the current analysis allows an examination of strata in which targeted treatment of these symptoms might be more beneficial. For example, of our study

population who experienced symptoms of depression and anxiety at baseline, only 13.6% of these individuals developed diabetes during follow-up, yet they accounted for 19.2% of new cases. Given these findings and the current diabetes epidemic, research to determine whether treating anxiety and depression in people exposed to other diabetes risk factors is effective in reducing the incidence rate may therefore prove to be useful.

However, we are unable to assume a direct causal link between symptoms of depression and anxiety and diabetes incidence. These results represent an 'excess fraction', rather than an 'etiologic fraction' (as defined by Greenland and Robins [37]). As noted by Flegal et al (2015), direct causal assumptions are not necessarily warranted when using PAFs [38] - as a result of mediational processes, different methods of intervening on a modifiable factor such as obesity may lead to different counterfactual outcomes, even if they achieve identical reductions in weight [39]. We were also unable to calculate *partial* or *summary attributable risks* as not all relative risks were greater than 1, and were therefore unable to report the summed contributions of each individual risk factor (i.e., 'column totals'). This highlighted the importance of the interaction between psychological factors and metabolic and behavioural factors in eliciting effects on diabetes onset.

In addition, as risk factors were measured simultaneously at baseline, it was not possible to assess mediating relationships or to differentiate between distal and proximal mechanisms of risk underlying these associations. Although the diabetes risk related to behavioural factors was relatively low in this study, these factors tend to confer disease risk through their subsequent effects on metabolic processes. For example, physical inactivity or smoking in individuals prior to baseline may have precipitated changes in metabolic health which persisted even if their behavioural risk status had changed by the time of assessment. It is therefore likely that we have underestimated the true impact of behavioural factors in the present study. Previous research on non-participation in the HUNT 3 study has also demonstrated that both mental health and

diabetes status are linked to study non-participation [40], and it is therefore possible that this study underestimated the true incidence rate of diabetes in the Norwegian population. As with all observational studies, our results are also vulnerable to the presence of unmeasured confounding.

It is worth noting that PAFs are highly influenced by the population prevalence of the risk factor of interest. In the aforementioned study of sugar sweetened beverages, the authors reported that while the PAF for diabetes cases in the USA was 8.7%, it was only 3.6% in the UK. These values may therefore vary in countries outside of Norway, where the prevalence of diabetes risk factors differs. Future research should quantify these effects within each target population of interest prior to using them to inform local health strategies.

4.4.3 Conclusions

Overall, the presence of the metabolic syndrome in conjunction with behavioural factors was the largest contributor to diabetes incidence in the Norwegian population. In addition, symptoms of depression and anxiety increased the percentage of excess diabetes cases attributable to common behavioural and metabolic factors, particularly in men. This study highlights the importance of risk factor clustering in diabetes onset, and is the first that we know of to quantify the excess fraction of incident diabetes associated with psychological risk factor interactions.

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Table 4.1. Baseline Characteristics of the HUNT 2-3 Cohort

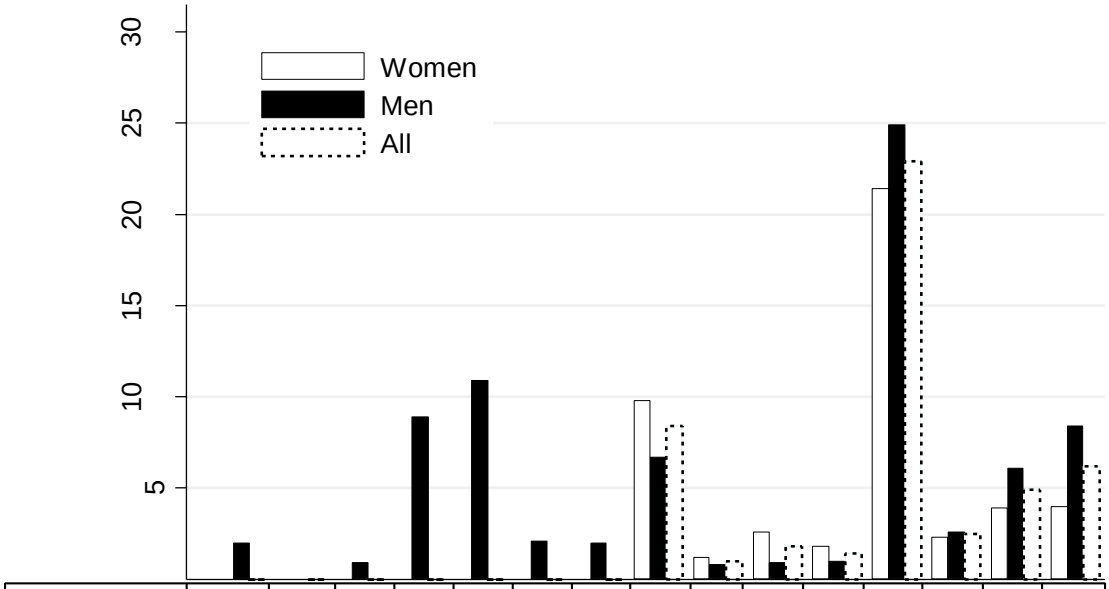
	WOMEN (n=20,014)	MEN (n=16,147)	ALL (N=36,161)
Demographic factors			
Age (mean, SD)	46.8 (13.7)	47.3 (13.1)	47.0 (13.4)
20-34	22.1%	19.5%	20.9%
35-44	24.3%	24.2%	24.3%
45-54	26.7%	27.9%	26.7%
55-64	17.0%	17.7%	17.0%
≥ 65	11.5%	10.6%	11.1%
Education (any post-secondary)	33.2%	30.1%	31.8%
Metabolic factors			
Central obesity*	47.9%	36.9%	42.9%
Hypertension†	46.2%	66.5%	55.3%
Triglycerides (high)	28.5%	48.5%	37.4%
HDL cholesterol (low)	24.9%	29.1%	26.8%
Plasma glucose (high)	2.1%	3.3%	2.6%
Metabolic syndrome present	20.2%	23.1%	21.5%
Behavioural factors			
Smoking (packyears, mean)	12.8 (10.2)	17.2 (13.6)	14.9 (12.1)
Former smoking (daily)	24.2%	33.5%	28.4%
Current smoking (daily)	27.9%	24.5%	26.4%
Physical inactivity‡	54.3%	48.2%	51.5%
Psychological factors			
Depression only	3.9%	2.3%	3.6%
Anxiety only	8.3%	5.5%	6.9%
Concurrent dep-anx	4.6%	2.9%	3.3%

* Waist circumference ≥ 94 cm for men; ≥ 80 for women

† Systolic blood pressure >130 mm Hg or diastolic >85 mm Hg

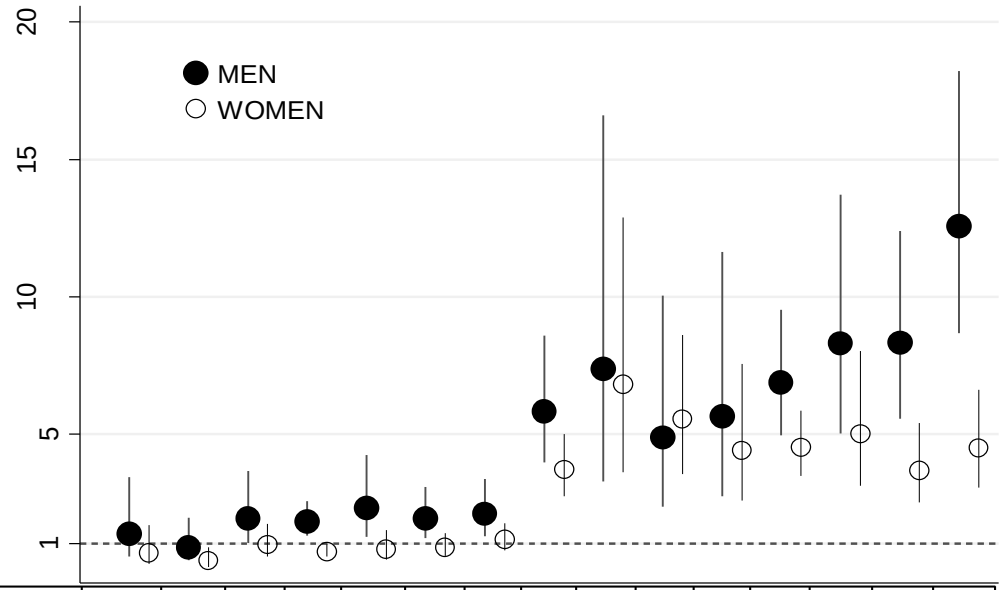
‡ Less than 150 minutes of moderate or 60 minutes of vigorous physical activity per week

Figure 4.1. Attributable fractions for Type 2 diabetes onset in Norwegian adults associated with multiple risk factors (N=36,161)



Depression	X				X				X				X		
Anxiety		X				X				X				X	
Dep-Anx			X				X				X				X
Behavioural Factors				X	X	X	X					X	X	X	X
Metabolic Syndrome								X	X	X	X	X	X	X	X

Figure 4.2. Relative Risk for Type 2 diabetes onset in Norwegian adults associated with multiple risk factors, by sex (N=36,161).



Depression	X				X				X				X		
Anxiety		X				X				X				X	
Dep-Anx			X				X				X				X
Behavioural Factors				X	X	X	X					X	X	X	X
Metabolic Syndrome								X	X	X	X	X	X	X	X

Table 4.2. Multivariate relative risks and population attributable fractions (PAF) for Type 2 diabetes onset in Norwegian adults associated with metabolic, behavioural and psychological risk factors (N=36,161)*

Behavioural†	MetSyn‡	Depression	Anxiety	Concurrent Dep-anx	# Exposed	Exposure prevalence	Diabetes cases	RR (95% CI)	PAF
0	0	0	0	0	7,602	21.02%	123	1.00	
0	0	1	0	0	803	2.22%	10	0.93 (0.49, 1.76)	-
0	0	0	1	0	1,461	4.04%	13	0.56 (0.32, 0.98)	-
0	0	0	0	1	1,319	3.65%	25	1.31 (0.85, 2.00)	-
1	0	0	0	0	11,309	31.27%	218	1.13 (0.91, 1.41)	-
1	0	1	0	0	1,256	3.47%	24	1.30 (0.85, 2.00)	-
1	0	0	1	0	2,447	6.77%	52	1.26 (0.91, 1.73)	-
1	0	0	0	1	2,435	6.73%	56	**1.49 (1.09, 2.04)**	1.4
0	1	0	0	0	1,561	4.32%	145	**4.42 (3.49, 5.60)**	8.4
0	1	1	0	0	135	0.37%	15	**6.87 (4.16, 11.35)**	1.0
0	1	0	1	0	278	0.77%	30	**4.88 (3.17, 7.53)**	1.8
0	1	0	0	1	255	0.71%	22	**5.46 (3.74, 7.97)**	1.4
1	1	0	0	0	3,493	9.66%	376	**5.26 (4.30, 6.42)**	22.9
1	1	1	0	0	342	0.95%	39	**6.13 (4.36, 8.62)**	2.5
1	1	0	1	0	766	2.12%	81	**5.29 (4.03, 6.93)**	4.9
1	1	0	0	1	699	1.93%	95	**7.47 (5.79, 9.64)**	6.2
TOTAL					36,161	100%	1324		50.5

* Adjusted for age and sex

† Physical inactivity and smoking factors

‡ Metabolic syndrome (as defined by the International Diabetes Federation [23])

Supplemental Table 4.1 Univariate relative risks of Type 2 diabetes incidence associated with primary study risk factors (N=36, 161)

	WOMEN (95% CI)	MEN (95% CI)	ALL (95% CI)*
DEMOGRAPHIC			
20-34	Ref	Ref	Ref
35-44	**3.25 (2.12, 4.97)**	**4.00 (2.65, 6.24)**	**3.61 (2.66, 4.91)**
45-54	**6.40 (4.29, 9.54)**	**7.12 (4.65, 10.90)**	**6.75 (5.05, 9.04)**
55-64	**10.89 (7.32, 16.21)**	**9.37 (6.10, 14.40)**	**10.10 (7.54, 13.52)**
≥ 65	**9.11 (6.02, 13.79)**	**9.63 (6.18, 15.01)**	**9.36 (6.91, 12.67)**
Education (no post-secondary)	**1.60 (1.29, 1.99)**	**1.41 (1.17, 1.71)**	**1.50 (1.30, 1.73)**
METABOLIC SYNDROME	**5.59 (4.72, 6.62)**	**5.07 (4.32, 5.96)**	**5.29 (4.71, 5.94)**
Central obesity	**6.84 (5.37, 8.70)**	**4.56 (3.82, 5.43)**	**5.31 (4.62, 6.11)**
Hypertension	**2.52 (2.08, 3.05)**	**1.86 (1.53, 2.26)**	**2.16 (1.89, 2.48)**
Triglycerides	**3.82 (3.25, 4.49)**	**3.17 (2.67, 3.77)**	**3.48 (3.09, 3.91)**
HDL Cholesterol	**3.37 (2.91, 3.91)**	**2.87 (2.47, 3.32)**	**3.11 (2.80, 3.45)**
Plasma glucose	**7.14 (5.84, 8.72)**	**5.22 (4.28, 6.37)**	**5.98 (5.19, 6.89)**
BEHAVIOURAL	1.10 (0.94, 1.28)	**1.78 (1.49, 2.13)**	**1.36 (1.21, 1.52)**
Physical Inactivity	**1.33 (1.12, 1.56)**	**1.76 (1.51, 2.06)**	**1.55 (1.38, 1.74)**
Smoking			
Former (daily)	0.92 (0.76, 1.11)	**1.66 (1.38, 2.01)**	**1.21 (1.06, 1.37)**
Current (daily)	1.09 (0.91, 1.32)	**1.63 (1.33, 2.00)**	**1.27 (1.11, 1.45)**
MENTAL HEALTH			
Depression only	1.24 (0.71, 2.17)	**1.65 (1.24, 2.20)**	**1.45 (1.18, 1.77)**
Anxiety only	1.28 (0.96, 1.70)	1.14 (0.60, 2.16)	1.19 (0.78, 1.82)
Concurrent Dep-Anx	1.05 (0.63, 1.73)	**2.07 (1.41, 3.05)**	**1.51 (1.11, 2.06)**
# of risk factors			
0 to 1 factors	Ref	Ref	Ref
2 factors	**2.62 (1.83, 3.75)**	**2.75 (1.68, 4.50)**	**2.62 (1.97, 3.50)**
3 factors	**5.62 (4.02, 7.85)**	**5.52 (3.48, 8.76)**	**5.43 (4.15, 7.10)**
4 or more factors	**11.60 (8.43, 15.96)**	**12.95 (8.36, 20.06)**	**11.89 (9.22, 15.34)**

Supplemental Table 4.2. Multivariate Relative Risk of Incident Type 2 Diabetes in HUNT 2-3 Cohort, by Sex

	Women (n=20,014)		Men (n=16,147)		All (n=36,161)	
	RR	95% CI	RR	95% CI	RR	95% CI
Demographic Factors						
Age						
20-34	Ref	Ref	Ref	Ref	Ref	Ref
35-44	2.42	1.57, 3.74	2.97	1.90, 4.63	2.68	1.97, 3.65
45-54	3.53	2.33, 5.36	4.45	2.90, 6.83	3.82	2.84, 5.14
55-64	4.23	2.76, 6.48	5.68	3.68, 8.77	4.72	3.50, 6.37
≥ 65	2.97	1.88, 4.70	5.41	3.43, 8.52	3.88	2.83, 5.32
Education (any post-secondary)	1.20	0.96, 1.50	1.19	1.00, 1.44	1.20	1.04, 1.38
Metabolic Factors						
Central obesity*	4.77	3.64, 6.25	3.31	2.75, 3.99	3.59	3.08, 4.18
Hypertension†	1.67	1.37, 2.04	1.49	1.22, 1.81	1.54	1.34, 1.77
Triglycerides	1.98	1.63, 2.41	1.79	1.47, 2.19	1.77	1.55, 2.03
HDL cholesterol	2.13	1.78, 2.54	1.84	1.57, 2.16	1.86	1.66, 2.10
Plasma glucose	3.68	2.40, 4.03	5.58	3.31, 6.90	4.05	3.55, 4.62
Behavioural Factors						
Smoking						
Never	Ref	Ref	Ref	Ref	Ref	Ref
Former (daily)	0.87	0.71, 1.07	1.43	1.18, 1.72	1.13	0.99, 1.29
Current (daily)	0.99	0.82, 1.22	1.50	1.22, 1.85	1.21	1.05, 1.39
Physical Inactivity‡	1.05	0.88, 1.24	1.38	1.18, 1.61	1.23	1.08, 1.36
Psychological Factors						
Depression only	1.14	0.63, 2.08	1.94	1.34, 2.83	1.37	1.01, 1.87
Anxiety only	1.24	0.92, 1.68	1.16	0.62, 2.16	1.16	0.76, 1.80
Concurrent Dep-Anx	0.93	0.56, 1.55	1.50	1.13, 2.00	1.36	1.10, 1.68

* Waist circumference ≥ 94 cm for men; ≥ 80 for women

† Systolic blood pressure >130 mm Hg or diastolic >85 mm Hg

‡ Less than 150 minutes of moderate or 60 minutes of vigorous physical activity per week

Supplemental Table 4.3. Multivariate relative risks and PAFs for Type 2 diabetes onset in Norwegian adults associated with metabolic, behavioural and psychological risk factors, women only (N=20,014)[a]

Behavioural[b]	MetSyn[c]	Depression	Anxiety	Concurrent Dep-anx	# exposed	Exposure prevalence	Diabetes cases	RR (95% CI)	PAF
0	0	0	0	0	4,202	21.00%	80	0.0	
0	0	1	0	0	481	2.40%	5	0.68 (0.28, 1.68)	-
0	0	0	1	0	811	4.05%	6	0.39 (0.17, 0.88)	-
0	0	0	0	1	798	3.99%	13	0.96 (0.54, 1.72)	-
1	0	0	0	0	6,185	30.90%	86	0.73 (0.54, 0.98)	-
1	0	1	0	0	824	4.12%	11	0.81 (0.43, 1.51)	-
1	0	0	1	0	1,342	6.71%	23	0.88 (0.56, 1.40)	-
1	0	0	0	1	1,469	7.34%	30	1.16 (0.76, 1.76)	-
0	1	0	0	0	905	4.52%	88	**3.70 (2.74, 4.99)**	9.8
0	1	1	0	0	70	0.35%	9	**6.80 (3.60, 12.89)**	1.2
0	1	0	1	0	162	0.81%	22	**4.40 (2.57, 7.56)**	2.6
0	1	0	0	1	150	0.75%	14	**5.53 (3.54, 8.62)**	1.8
1	1	0	0	0	1,680	8.39%	180	**4.51 (3.48, 5.84)**	21.4
1	1	1	0	0	185	0.92%	19	**5.00 (3.11, 8.02)**	2.3
1	1	0	1	0	394	1.97%	35	**3.67 (2.50, 5.39)**	3.9
1	1	0	0	1	356	1.78%	34	**4.49 (3.06, 6.60)**	4.0
TOTAL					20,014	100%	655	-	47.0

[a] Adjusted for age and sex

[b] Physical inactivity and smoking factors

[c] Metabolic syndrome (as defined by the International Diabetes Federation (24))

Supplemental Table 4.4. Multivariate relative risks and PAFs for Type 2 diabetes onset in Norwegian adults associated with metabolic, behavioural and psychological risk factors, men only (N=16,147)[a]

Behavioural[b]	MetSyn[c]	Depression	Anxiety	Comorbid Dep-anx	# exposed	Exposure prevalence	Diabetes cases	RR (95% CI)	PAR
0	0	0	0	0	3,400	21.03%	43	0.0	-
0	0	1	0	0	322	1.99%	5	1.37 (0.55, 3.43)	2.0
0	0	0	1	0	650	4.03%	7	0.88 (0.40, 1.95)	-
0	0	0	0	1	521	3.23%	12	**1.94 (1.03, 3.65)**	0.9
1	0	0	0	0	5,124	31.73%	132	**1.82 (1.30, 2.56)**	8.9
1	0	1	0	0	432	2.68%	13	**2.30 (1.25, 4.23)**	10.9
1	0	0	1	0	1,105	6.84%	29	**1.93 (1.21, 3.07)**	2.1
1	0	0	0	1	966	5.98%	26	**2.08 (1.29, 3.37)**	2.0
0	1	0	0	0	656	4.06%	57	**5.83 (3.96, 8.58)**	6.7
0	1	1	0	0	65	0.40%	6	**7.37 (3.28, 16.59)**	0.8
0	1	0	1	0	116	0.72%	8	**4.85 (2.35, 10.01)**	0.9
0	1	0	0	1	105	0.65%	8	**5.64 (2.74, 11.63)**	1.0
1	1	0	0	0	1,813	11.23%	196	**6.87 (4.96, 9.52)**	24.9
1	1	1	0	0	157	0.97%	20	**8.29 (5.02, 13.70)**	2.6
1	1	0	1	0	372	2.30%	46	**8.30 (5.56, 12.39)**	6.1
1	1	0	0	1	343	2.12%	61	**12.57 (8.67, 16.22)**	8.4
TOTAL					16,147	100%	669	-	78.2

[a] Adjusted for age and sex

[b] Physical inactivity and smoking factors

[c] Metabolic syndrome (as defined by the International Diabetes Federation (24))

Supplemental Table 4.5 Comparison of Miettinen and Levin's formulas for calculating population attributable fractions (PAFs)

Behavioural	MetSyn	Depression	Anxiety	Concurrent Dep-anx	ALL		WOMEN		MEN	
					Miettinen	Levin	Miettinen	Levin	Miettinen	Levin
0	0	0	0	0					-	
0	0	1	0	0	-	-	-	-	2.0	0.7
0	0	0	1	0	-	-	-	-	-	-
0	0	0	0	1	-	-	-	-	0.9	2.9
1	0	0	0	0	-	-	-	-	8.9	20.6
1	0	1	0	0	-	-	-	-	10.9	3.4
1	0	0	1	0	-	-	-	-	2.1	6.0
1	0	0	0	1	1.4	3.2	-	1.1	2.0	6.1
0	1	0	0	0	8.4	12.9	9.8	10.9	6.7	16.4
0	1	1	0	0	1.0	2.1	1.2	2.0	0.8	2.5
0	1	0	1	0	1.8	2.9	2.6	2.7	0.9	2.7
0	1	0	0	1	1.4	3.1	1.8	3.3	1.0	2.9
1	1	0	0	0	22.9	29.1	21.4	22.7	24.91	39.7
1	1	1	0	0	2.5	4.7	2.3	3.5	2.6	6.6
1	1	0	1	0	4.9	8.3	3.9	5.0	6.1	14.4
1	1	0	0	1	6.2	11.1	4.0	5.8	8.4	19.7
TOTAL					**50.5**	**77.4**	**47.0**	**55.9**	**78.2**	**144.6**

REFERENCES

1. International Diabetes Federation (2015) IDF Diabetes Atlas, 7th Edition. International Diabetes Federation, Brussels, Belgium

2. Moulton CD, Pickup JC, Ismail K (2015) The link between depression and diabetes: the search for shared mechanisms. Lancet Diabetes Endocrinol 3:461–471. doi: 10.1016/S2213-8587(15)00134-5

3. Willis T (1971) Diabetes: a medical odyssey. New York, Tuckahoe

4. Luppino FS, de Wit LM, Bouvy PF, et al (2010) Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. Arch Gen Psychiatry 67:220–9. doi: 10.1001/archgenpsychiatry.2010.2

5. Roshanaei-Moghaddam B, Katon WJ, Russo J (2009) The longitudinal effects of depression on physical activity. Gen Hosp Psychiatry 31:306–315. doi: 10.1016/j.genhosppsych.2009.04.002

6. Khambaty T, Stewart JC, Muldoon MF, Kamarck TW (2014) Depressive symptom clusters as predictors of 6-year increases in insulin resistance: data from the Pittsburgh Healthy Heart Project. Psychosom Med 76:363–9. doi: 10.1097/PSY.0000000000000063

7. Demakakos P, Zaninotto P, Nouwen A (2014) Is the association between depressive symptoms and glucose metabolism bidirectional? Evidence from the English Longitudinal Study of Ageing. Psychosom Med 76:555–61. doi: 10.1097/PSY.0000000000000082

8. Young EA, Abelson JL, Cameron OG (2004) Effect of comorbid anxiety disorders on the Hypothalamic-Pituitary-Adrenal axis response to a social stressor in major depression. Biol Psychiatry 56:113–120. doi: 10.1016/j.biopsych.2004.03.017

9. Hou R, Baldwin DS (2012) A neuroimmunological perspective on anxiety disorders. Hum Psychopharmacol Clin Exp 27:6–14. doi: 10.1002/hup.1259

10. Hirschfeld RMA (2001) The Comorbidity of Major Depression and Anxiety Disorders: Recognition and Management in Primary Care. Prim Care Companion J Clin Psychiatry 3:244–254.

11. Cosgrove MP, Sargeant LA, Griffin SJ (2008) Does depression increase the risk of developing type 2 diabetes? Occup Med (Chic Ill) 58:7–14. doi: 10.1093/occmed/kqm105

12. Al Tunaiji H, Davis JC, Mackey DC, Khan KM (2014) Population attributable fraction of type 2 diabetes due to physical inactivity in adults: a systematic review. BMC Public Health 14:469. doi: 10.1186/1471-2458-14-469

13. Wang Y, Rimm EB, Stampfer MJ, et al (2005) Comparison of abdominal adiposity and overall obesity in predicting risk of type 2 diabetes among men. Am J Clin Nutr 81:555–63.

14. Imamura F, O'Connor L, Ye Z, et al (2015) Consumption of sugar sweetened beverages, artificially sweetened beverages, and fruit juice and incidence of type 2 diabetes: systematic review, meta-analysis, and estimation of population attributable fraction. BMJ 351:h3576. doi: 10.1136/BMJ.H3576

15. Ford ES (2005) Risks for All-Cause Mortality, Cardiovascular Disease, and Diabetes Associated With the Metabolic Syndrome. Diabetes Care 28:

16. Sandhu MS, Weedon MN, Fawcett KA, et al (2007) Common variants in WFS1 confer risk of type 2 diabetes. Nat Genet 39:951–953. doi: 10.1038/ng2067

17. Genest J, Cohn JS (1995) Clustering of cardiovascular risk factors: Targeting high-risk individuals. Am J Cardiol 76:8A–20A. doi: 10.1016/S0002-9149(05)80010-4

18. Jousilahti P, Toumilehto J, Vartiainen E, et al (1995) Importance of risk factor clustering in coronary heart disease mortality and incidence in eastern Finland. J Cardiovasc Risk 2:63–70.

19. Kannel WB, McGee D, Gordon T (1976) A general cardiovascular risk profile: the Framingham Study. Am J Cardiol 38:46–51.

20. Chang M, Hahn RA, Teutsch SM, Hutwagner LC (2001) Multiple risk factors and population attributable risk for ischemic heart disease mortality in the United States, 1971–1992. J Clin Epidemiol 54:634–644. doi: 10.1016/S0895-4356(00)00343-7

21. Laaksonen MA, Knekt P, Rissanen H, et al (2010) The relative importance of modifiable potential risk factors of type 2 diabetes: a meta-analysis of two cohorts. Eur J Epidemiol 25:115–124. doi: 10.1007/s10654-009-9405-0

22. Krokstad S, Langhammer A, Hveem K, et al (2013) Cohort Profile: the HUNT Study, Norway. Int J Epidemiol 42:968–77. doi: 10.1093/ije/dys095

23. Alberti KGMM, Zimmet P, Shaw J (2006) Metabolic syndrome-a new world-wide definition. A Consensus Statement from the International Diabetes Federation. Diabet Med 23:469–480. doi: 10.1111/j.1464-5491.2006.01858.x

24. World Health Organization (2010) Global recommendations on physical activity for health. Glob Recomm Phys Act Heal 58.

25. Wannamethee SG, Shaper AG, Perry IJ (1978) Smoking as a Modifiable Risk Factor for Type 2 Diabetes in Middle-Aged Men. Diabetes Care 24:1590–1595.

26. Søgaard A, Bjelland I, Tell G, Røysamb E (2003) A comparison of the CONOR Mental Health Index to the HSCL-10 and HADS. Nor. Epidemiol.

27. Harrell FE (2001) General Aspects of Fitting Regression Models. pp 11–40

28. Royston P (2004) Multiple Imputation of Missing Values. The Stata Journal, 4 (3), 227–241.

29. Hanley JA (2001) A heuristic approach to the formulas for population attributable fraction. J Epidemiol Community Health 55:508–14. doi: 10.1136/jech.55.7.508

30. Levin ML (1953) The occurrence of lung cancer in man. Acta Unio Int Contra Cancrum 9:531–41.

31. Mezuk B, Eaton W, Albrecht S, Golden S (2008) Depression and type 2 diabetes over the lifespan a meta-analysis. Diabetes Care

32. Goodpaster BH, Krishnaswami S, Harris TB, et al (2005) Obesity, Regional Body Fat Distribution, and the Metabolic Syndrome in Older Men and Women. Arch Intern Med 165:777. doi: 10.1001/archinte.165.7.777

33. Will JC, Galuska DA, Ford ES, et al (2001) Cigarette smoking and diabetes mellitus: evidence of a positive association from a large prospective cohort study. Int J Epidemiol 30:540–546. doi: 10.1093/ije/30.3.540

34. Cherrington A, Wallston KA, Rothman RL (2010) Exploring the relationship between diabetes self-efficacy, depressive symptoms, and glycemic control among men and women with type 2 diabetes. J Behav Med 33:81–9. doi: 10.1007/s10865-009-9233-4

35. Vogelzangs N, Beekman ATF, de Jonge P, Penninx BWJH (2013) Anxiety disorders and

inflammation in a large adult cohort. Transl Psychiatry 3:e249. doi: 10.1038/tp.2013.27

36. Naicker K, Johnson JA, Skogen JC, et al (2017) Type 2 Diabetes and Comorbid Symptoms of Depression and Anxiety: Longitudinal Associations With Mortality Risk. Diabetes Care

37. Greenland S, Robins JM (1988) Conceptual problems in the definition and interpretation of attributable fractions. Am J Epidemiol 128:1185–97. doi: 10.1093/OXFORDJOURNALS.AJE.A115073

38. Flegal KM, Panagiotou OA, Graubard BI (2015) Estimating population attributable fractions to quantify the health burden of obesity. Ann Epidemiol 25:201–7. doi: 10.1016/j.annepidem.2014.11.010

39. Hernán MA, Taubman SL (2008) Does obesity shorten life? The importance of well-defined interventions to answer causal questions. Int J Obes 32:S8–S14. doi: 10.1038/ijo.2008.82

40. Langhammer A, Krokstad S, Romundstad P, et al (2012) The HUNT study: participation is associated with survival and depends on socioeconomic status, diseases and symptoms. BMC Med Res Methodol 12:143. doi: 10.1186/1471-2288-12-143

Appendix 4A. Sensitivity analysis comparing imputed versus unimputed multivariate relative risks for Type 2 diabetes onset in Norwegian adults associated with metabolic, behavioural and psychological risk factors (N=36,161)*

Behavioural†	MetSyn‡	Depression	Anxiety	Concurrent Dep-anx	UNIMPUTED RR (95% CI)	IMPUTED RR (95% CI)
0	0	0	0	0	1.00	1.00
0	0	1	0	0	1.10 (0.87, 1.43)	0.93 (0.49, 1.76)
0	0	0	1	0	0.78 (0.75, 1.02)	0.56 (0.32, 0.98)
0	0	0	0	1	0.95 (0.79, 1.13)	1.31 (0.85, 2.00)
1	0	0	0	0	0.98 (0.85, 1.20)	1.13 (0.91, 1.41)
1	0	1	0	0	1.10 (0.61, 1.17)	1.30 (0.85, 2.00)
1	0	0	1	0	0.98 (0.77, 1.03)	1.26 (0.91, 1.73)
1	0	0	0	1	**1.28 (1.03, 1.86)**	**1.49 (1.09, 2.04)**
0	1	0	0	0	**4.59 (4.21, 5.02)**	**4.42 (3.49, 5.60)**
0	1	1	0	0	**6.38 (5.17, 7.40)**	**6.87 (4.16, 11.35)**
0	1	0	1	0	**5.10 (4.63, 5.81)**	**4.88 (3.17, 7.53)**
0	1	0	0	1	**5.78 (5.08, 6.56)**	**5.46 (3.74, 7.97)**
1	1	0	0	0	**4.97 (4.37, 6.12)**	**5.26 (4.30, 6.42)**
1	1	1	0	0	**5.97 (4.28, 6.76)**	**6.13 (4.36, 8.62)**
1	1	0	1	0	**5.50 (4.07, 5.98)**	**5.29 (4.03, 6.93)**
1	1	0	0	1	**7.09 (5.58, 8.66)**	**7.47 (5.79, 9.64)**

* Adjusted for age and sex

† Physical inactivity and smoking factors

‡ Metabolic syndrome (as defined by the International Diabetes Federation [23])

Appendix 4B. STROBE Statement

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	90
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	91
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	92-93
Objectives	3	State specific objectives, including any prespecified hypotheses	93
Methods			
Study design	4	Present key elements of study design early in the paper	94
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	94
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	94
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	94-97
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	94-97
Bias	9	Describe any efforts to address potential sources of bias	96-97
Study size	10	Explain how the study size was arrived at	94
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	94-96
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	96-97
		(*b*) Describe any methods used to examine subgroups and interactions	96-97
		(*c*) Explain how missing data were addressed	96-97
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	94,96
		(*e*) Describe any sensitivity analyses	97

Appendix 4B. STROBE Statement (continued)

Results			**Page**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	94
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	98, 105
		(b) Indicate number of participants with missing data for each variable of interest	85
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	9, 24
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	98-99, 108-109
		(*b*) Report category boundaries when continuous variables were categorized	110
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	108, 111-112
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	113, 117
Discussion			
Key results	18	Summarise key results with reference to study objectives	100
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	100-105
Generalisability	21	Discuss the generalisability (external validity) of the study results	104
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	105

Appendix 4C. Screenshot of letter confirming manuscript submission to *Diabetes Care*

01-Sep-2017

DC17-1839 - "Population attributable fractions for Type 2 diabetes: An examination of multiple risk factors including symptoms of depression and anxiety" has been submitted to Diabetes Care.

Dear Dr. Colman:

Thank you for submitting your work to Diabetes Care. Your manuscript has been successfully submitted and is presently being given full consideration for publication. Please refer to the above manuscript number in all future correspondence.

If you have not already done so, please e-mail or fax the completed manuscript submission form to the Editorial Office (317-547-4656; diabetescare@diabetes.org) at your earliest convenience. The manuscript submission form can be found at http://mc.manuscriptcentral.com/diabetescare or with the instructions for authors at http://care.diabetesjournals.org.

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If you have any questions or need assistance, please do not hesitate to contact us at diabetescare@diabetes.org.

Thank you once again,

Lyn Reynolds, Director, Editorial Office
Shannon Potts, Peer Review Manager

Appendix 4D. Ethical approval from HUNT Study committee for manuscript publication

NTNU

Fakultet for medisin og helsevitenskap
Institutt for samfunnsmedisin og sykepleie

Vår dato 21.06.2017
Deres dato

Vår referanse 2014/22653/TRS
Deres referanse

Børge Sivertsen
Avdeling for helsefremmende arbeid
Folkehelseinstituttet
5015 Bergen

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Forfattere: *Naicker K, Øverland S, Johnson JA, Manuel D, Skogen JC, Siversen B, Colman I*
Datert: *120617*

Publikasjonsutvalget har vurdert manuset ut fra den inngåtte avtalen om analyserettigheter til HUNT-data og retningslinjene for forvaltning og bruk av data og har ingen innvendinger til at manuset publiseres slik det er fremlagt.

Publikasjonsutvalget ønsker kopi av artikkelen så snart den foreligger.

Med hilsen

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CHAPTER 5:

SYMPTOMS OF ANXIETY AND DEPRESSION IN TYPE 2 DIABETES: CROSS-SECTIONAL ASSOCIATIONS WITH CLINICAL DIABETES MEASURES AND SELF-MANAGEMENT OUTCOMES

Preface

The purpose of the study presented in this chapter was to estimate the associations between symptoms of depression, anxiety and a comprehensive set of key clinical and self-management diabetes outcomes. The main study hypotheses were: 1) that symptoms of depression, anxiety, and concurrent depression-anxiety would be independently associated with poor glycemic control, 2) that the latter associations would be stronger in men than in women, and 3) that symptoms of depression and anxiety would be differentially associated with diabetes self-care outcomes in men and women.

The article presented in this chapter was published in *Psychoneuroendocrinology* in October 2017, and is cited as: Naicker, K., Øverland, S., Johnson, J. A., Manuel, D., Skogen, J. C., Sivertsen, B., & Colman, I. (2017). Symptoms of anxiety and depression in type 2 diabetes: Associations with clinical diabetes measures and self-management outcomes in the Norwegian HUNT study. *Psychoneuroendocrinology*, *84*, 116-123 (see Appendix 5B for journal acceptance letter). All tables and figures are marked as primary and supplementary corresponding to the submitted version. Additional supporting documents, including sensitivity analyses and ethical approval, are included in appendices at the end of this chapter.

Contribution Statement: I was responsible for generating the study hypothesis and design, with guidance from supervisors and co-authors. I conducted the necessary statistical analysis, created all of the tables and figures, and drafted the final manuscript. I also responded to all comments arising from the peer review process.

ABSTRACT

Background/Objective: Depression is strongly linked to poor outcomes in Type 2 diabetes, and is shown to influence both patient behaviour and underlying biological processes. The objective of this study was to determine if symptoms of depression and anxiety are differentially associated with clinical diabetes measures and self-management behaviours in individuals with Type 2 diabetes, and whether these associations vary by patient sex.

Research Design and Methods: A cross-sectional analysis using data from 2,035 adults with Type 2 diabetes in the Nord-Trøndelag Health Study. Multivariate logistic regression was used to explore associations between symptoms of depression and anxiety and waist girth, HDL cholesterol, systolic blood pressure, triglycerides, c-reactive protein, glycemic control, diet adherence, exercise, glucose monitoring, foot checks for ulcers, and the subjective patient experience. Analyses were stratified by sex.

Results: Depressive symptoms were associated with a lower likelihood of avoiding saturated fats (OR=0.20 [95% CI: 0.06, 0.68]) and increased odds of physical inactivity (OR=1.69 [95% CI: 1.37, 2.72]. Anxious symptoms were associated with increased odds of eating vegetables (OR=1.66 [95% CI: 1.02, 2.73], and an over two-fold increase of feeling that having diabetes is difficult. In women, anxiety was associated with elevated c-reactive protein levels (OR=1.57 [95% CI: 1.05, 2.34]). In men, depressive symptoms were associated with elevated HbA1c (OR=5.00 [95% CI: 1.15, 8.23).

Conclusion/Interpretation: Symptoms of depression and anxiety were differentially associated with some key diabetes-related measures. Our results suggest sex-specific differences with respect to two important clinical outcomes (i.e., anxiety and CRP in women and depression and glycemic control in men). These findings should alert practitioners to the importance of detection and management of psychological symptoms in individuals with Type 2 diabetes.

5.1 INTRODUCTION

Type 2 diabetes represents an increasing global health challenge, due to its growing prevalence worldwide and the chronic complications and functional impairment associated with this condition. Patients with Type 2 diabetes frequently suffer from unipolar depression and anxiety disorders, at rates at least double those observed in diabetes-free populations [1, 2]. There is increasing evidence that psychosomatic processes contribute to a range of Type 2 diabetes outcomes, and unipolar depression has been shown to influence the management and prognosis of Type 2 diabetes through adverse effects on factors such as glycemic control [3], self-care behaviours [4], and body mass index [5]. In line with this, the presence of comorbid depression in diabetes patients often leads to increased health-care costs, higher risks of vascular complications [6, 7], and excess mortality rates [8].

Although anxiety disorders often co-occur with depression, anxiety is a far less well understood comorbidity of diabetes. One notable limitation of studies in this area is that they tend to focus on one disorder type at a time, while failing to account for the presence of the other [9–12]. This makes it particularly challenging to assess the scope of the impact of anxiety disorders (or indeed, depression) on diabetes-related outcomes. Both psychiatric disorders share a significant overlap of features (e.g., generalized distress and low serotonin levels [13]), and over 40% of Type 2 diabetes patients presenting with major or minor depression in primary care settings are diagnosed with a concurrent anxiety disorder [1]. However, depression and anxiety also display important phenotypic differences. Whereas depression is uniquely associated with anhedonia and physiological responses such as lethargy and fatigue, anxiety is marked by excessive worry and physiologic hyperarousal such as trembling, sweating, and muscle tension [14, 15]. Evidence suggests that, like depression, anxiety may have important associations with diabetes outcomes such as an increased risk of hypertension, inflammation, and glycemic control [16,

17]. It is also evident that important sex differences may exist with respect to these associations; for example, depression has been linked to poor glycemic control in men, but not women [3]. Similar results have been noted with respect to anxiety disorders and risks of heightened inflammation in men [16].

The experience of concurrent symptoms of anxiety and depression is also associated with worse treatment outcomes than either disorder alone, including poorer adherence to treatment, higher costs, and lower quality of life [18]. Recent research in patients with cancer demonstrated that concurrent anxiety-depression was present in over 60% of patients with depression, and that this phenotype was only associated with specific cancer subtypes [19]. To our knowledge, no similar research has been conducted with respect to affective symptom phenotypes and diabetes outcomes. By failing to adequately differentiate between these phenotypes, existing studies may link complications related to the presence of anxiety or its correlates erroneously to depression, or vice versa. A proper understanding of these relationships may inform the development of more refined and integrated approaches to treatment in the future, as certain affective symptom phenotypes may be more relevant to specific Type 2 diabetes outcomes, and these associations could vary across patient populations.

The purpose of this study was to investigate the mutually exclusive associations between symptoms of depression and/or anxiety and several important clinical and behavioural outcomes in Type 2 diabetes, as well as to document any variations in patient outcomes by sex.

5.2 METHODS

5.2.1 Data Source and Participants

This was a cross-sectional study which used data from the third wave of the Norwegian Nord-Trøndelag Health Study (HUNT). The HUNT study is a large population-based survey conducted over three waves, in 1984/86 (HUNT 1), 1995/97 (HUNT 2) and 2006/08 (HUNT 3). The survey was conducted using a simple non-stratified design that included every adult resident of the Nord-Trøndelag County. The initial HUNT study was primarily established to address arterial hypertension, diabetes, tuberculosis screening and quality of life, and includes an advanced biobank initiative established in the third wave of the survey [20]. For the HUNT 3 wave, 93 860 individuals aged 20 years or older received a personal invitation to participate between October 2006 to June 2008, based on monthly updated census data. Of these, 50 847 (54.1%) participated by completing the initial questionnaire, and 2,255 individuals who self-reported having diabetes were invited to participate in a detailed diabetes sub-study. The HUNT cohort profile and methodology has been well-described elsewhere [20], and a detailed analysis of the non-responders from HUNT 3 is also available [21].

Our sample consisted of 2,035 individuals who were confirmed in the sub-study to have Type 2 diabetes, based on results of three repeated laboratory tests (fasting plasma glucose, oral glucose tolerance, and serum HbA1c levels). All individuals were additionally confirmed to be anti-glutamic acid decarboxylase and anti-insulinoma-associated negative (to exclude latent autoimmune diabetes in adults (LADA) cases), and confirmed as having not begun insulin treatment within one year of diagnosis to exclude Type 1 cases.

5.2.2 Exposure Variables

Our three primary exposures of interest were the participant's current experience of high levels of 1) depressive symptoms only, 2) anxious symptoms only, and 3) comorbid anxious-depressive symptoms, each compared to a referent group experiencing no or low levels of affective symptoms. The exposure categories were mutually exclusive; each category excluded individuals who were experiencing symptoms of the other.

These symptoms were measured in HUNT 3 using a 7-item mental health index (CONOR-MHI). This tool is a modified version of the General Health Questionnaire and the Hopkin's Symptoms Checklist (HSCL), and consists of widely validated scale items. It was further evaluated against both the HSCL-10 and Hospital Anxiety and Depression Scales (HADS) within both the HUNT Study and Oslo Health Study cohorts, and found to have strong accuracy when tested against each of these scales (AUC=0.902 and AUC=0.909, respectively) [22]. The internal consistency of the CONOR-MHI was also high across other large Norwegian datasets (Cronbach alpha $\geq$0.80) [22].

Individuals were asked "In the last two weeks, have you felt...?" with respect to the following items (translated from the original Norwegian): 'Calm and confident'; 'Nervous and restless'; 'Troubled by anxiety'; 'Happy and optimistic'; 'Irritable'; 'Down or depressed'; and 'Lonely'. The response set of each item consisted of four options: 1) "No", 2) "A little", 3) "A good amount", and 4) "Very much". The former three items loaded onto the anxiety factor and the latter three onto the depression factor, with the optimism factor excluded (see 'Statistical Analysis' below). Individuals were classified as having "high" symptom levels if their mean scores on these items fell above the recommended cut-off of 2.15, and as having "low or none" if their mean scores fell below this value [22].

5.2.3 Outcome Variables

Our outcomes of interest included a selection of clinical measures that are considered important in diabetes control and complications, as well as behavioural measures related to optimal disease self-management.

Seven clinical outcomes were dichotomized in accordance with either the International Diabetes Federation definition of the metabolic syndrome [23], or other commonly used metrics of glycemic control [24], as follows:

- Waist circumference: ≥ 94 cm for men; ≥ 80 for women
- Triglyceride levels: ≥ 150 mg/dL (1.7 mmol/L)
- HDL cholesterol: < 40 mg/dL (1.03 mmol/L) for men; < 50 mg/dL (1.29 mmol/L) for women
- Systolic blood pressure: ≥ 130 mm Hg
- Hemoglobin A1C (HbA1C): > 7.0% (53 mmol/mol)
- Random plasma glucose levels: ≥ 11.1 mmol/L

Serum C-reactive protein was also included, due to its associations with inflammation and cardiovascular disease outcomes [25], and growing evidence for its association with depression [26]. A cut-point of 3.0 mg/l was used, as recommended by the American Heart Association, corresponding roughly to the upper tertile of serum CRP in our sample [25].

Seven self-management variables were also included. These related to health behaviours, diabetes-specific tasks, and the subjective experience of having diabetes, and were defined as follows:

- Glucose monitoring at home (participants were asked *"At home, do you measure how much sugar (glucose) you have in your blood (blood sugar)?"* by themselves or someone else)
- Checking feet for sores or ulcers (participants were asked *"Are your feet examined regularly by yourself/pedicurist/home care nurse/other?"*)
- Exercise < 2-3 times per week (participants were asked *"How often do you exercise? By exercise we mean going for walks, skiing, swimming and working out/sports."*)
- Diet adherence: saturated fats (participants responded to *"On most days I try to avoid saturated fat."*)
- Diet adherence: eating vegetables (participants responded to *"On most days I eat a lot of vegetables."*)
- Subjective experience: diet adherence (participants responded to *"I see it as a problem I cannot eat what I want."*)
- Subjective experience: difficulty with diabetes (participants responded to *"I find having diabetes difficult."*)

5.2.4 Covariates

Covariates included age, sex, marital status, current smoking status, pack years smoked, alcohol consumption, family history of diabetes, and comorbid chronic conditions. Age was included as a continuous covariate. Marital status was included due to its potential effects on the completion of self-management tasks, and defined as "married/common-law" or "single/widowed/divorced". Current smoking status was categorized as "yes", "no" or "former." Pack years smoked were defined as years of daily or occasional smoking, multiplied by the number of packs smoked per day. Alcohol consumption was defined as the mean number of drinks consumed weekly, and immediate family history of diabetes (i.e., siblings or parents)

was included as a binary variable. The presence of one or more additional self-reported chronic physical condition was also included as a binary variable (i.e., the presence of any cancer, cardiac disease, asthma, allergies, epilepsy, or thyroid disease).

5.2.5 Statistical Analysis

To ascertain the structural validity of the CONOR mental health index, we performed a confirmatory factor analysis on the 7-item index using weighted least squares means and variance adjusted estimator (WLSMV). One factor, two-factor and bi-factor models were tested. The Chi-squared, comparative fit index (CFI), Tucker Lewis index (TLI), and root mean square error of approximation (RMSEA) statistics were calculated to determine model fit. This analysis was conducted using MPlus Version 7.

Univariate and multivariate logistic regression models were then used to examine mutually exclusive associations between anxiety, depression and comorbid anxiety-depression exposures and each study outcome. Each exposure therefore served as an independent variable for 14 different regression models, corresponding to the outcomes described above. All variables were checked for outliers and subsequently dichotomized. In addition, variance inflation factors (VIFs) were calculated for adjusted models and multicollinearity was determined not to be an issue. Models were built using backward selection, and all variables significant at the $\alpha=0.10$ level were included in the final adjusted models. Models examining clinical outcomes were additionally adjusted for all other clinical outcomes in the table. A formal test for interaction by sex was included in each model of the overall sample, and analyses were subsequently stratified by sex. All regression analyses were conducted using STATA 14.0.

Prior to regression analysis, the rate of missingness of each variable was calculated and patterns of missingness were examined. Variables appeared to be missing at random (MAR). Logistic

regression was then performed using imputation of missing covariate values, under the multiple imputation by chained equations (MICE) method [27]. This technique created 30 imputed datasets, from which reported estimates were computed. The amount of data missing was low on almost all covariates. Due to the simple sampling design of the HUNT survey, sampling weights were not recommended nor used.

5.3 RESULTS

We included 2,035 participants confirmed to have Type 2 diabetes and who completed the items on mental health (CONOR-MHI). Of our total study sample, 839 (41.2%) individuals were above the cut-off for affective symptoms (i.e., depression only (n=258), anxiety only (n=402), and concurrent depression and anxiety (n= 179)) (Table 5.1). Individuals experiencing high levels of affective symptoms had higher rates of physical inactivity and smoking (Table 5.1); in addition, while more women than men had either depressive or anxious symptoms only, slightly more than half of those individuals with comorbid depression-anxiety were men. Alcohol consumption, pack years smoked, and chronic physical conditions did not meet the a priori threshold for inclusion (i.e., $p<0.10$) in any of the adjusted models, and were therefore not retained in any of the analyses described below.

Overall, depressive symptoms were associated in unadjusted models with serum c-reactive protein and the subjective diabetes experience (Table 5.2). After adjustment for all other factors, symptoms of depression were associated with a lower likelihood of avoiding saturated fats (OR=0.20 [95% CI: 0.06, 0.68]), and a more than two-fold increased odds of feeling that diabetes is difficult (OR=2.41 [95% CI: 1.10, 4.30]). Anxious symptoms were associated with c-reactive protein, glucose, exercise, and the subjective diabetes experience in unadjusted models. After adjustment, anxiety was associated with a lowered risk of high blood pressure (OR=0.71 [95% CI: 0.52, 0.97]), increased odds of having high blood glucose (OR=1.87 [95% CI: 1.32, 2.63]), increased odds of eating vegetables (OR=1.66 [95% CI: 1.02, 2.73], increased odds of physical inactivity (OR=1.57, [95% CI: 1.08, 2.27]), and an over two-fold increase in the likelihood of feeling that diet adherence is problematic (OR=2.66 [95% CI: 1.71, 4.16]) or the feeling that having diabetes is difficult (OR=2.56 [95% CI: 1.68, 3.91]). Lastly, concurrent anxious and depressive symptoms were associated with high c-reactive protein levels, physical

inactivity, and the subjective diabetes experience in unadjusted models. After adjustment, concurrent anxious-depressive symptoms were associated with physical inactivity (OR=1.55 [95% CI: 1.03, 2.44]), an over two-fold increase in the likelihood of feeling that diet adherence is problematic (OR=2.26 [95% CI: 1.30, 3.95]), and the feeling that having diabetes is difficult (OR=2.26 [95% CI: 1.30, 3.92]). A significant interaction by sex was observed with respect to symptoms of anxiety and CRP levels, as well as saturated fat consumption (Table 5.2). In addition, a significant interaction by sex was observed with respect to both symptoms of depression and concurrent depression-anxiety and both measures of glycemic control (i.e., HbA1c and serum glucose).

When stratified by sex, symptoms of depression, anxiety and comorbid depression-anxiety were associated with physical inactivity and the subjective diabetes experience in both women (Table 5.3) and men (Table 5.4). Across sexes, comorbid anxious-depressive symptoms were associated with a three-fold increase in the odds of feeling that diet adherence is problematic (women: OR=3.32 [95% CI: 1.78, 6.17]; men: OR=2.95 [95% CI: 1.43, 6.09]), higher than either symptom group alone. The odds of feeling that having diabetes is difficult were greatest in women experiencing concurrent anxious-depressive symptoms (OR=3.90 [95% CI: 2.00, 7.60]), and in men experiencing high levels of anxious symptoms (OR=3.39 [95% CI: 2.08, 5.52]). Anxious symptoms alone were associated with high serum CRP levels in women (OR=1.57 [95% CI: 1.05, 2.34]), as well as a greater tendency to report avoiding saturated fats in women (OR=1.17 [1.17, 1.94]). In men, all affective symptoms were associated with high non-fasting glucose levels, with the greatest likelihood of high glucose occurring in men experiencing concurrent anxious-depressive symptoms (OR=3.20 [95% CI: 1.64, 6.20]). Depressive symptoms were similarly associated with elevated HbA1C levels in men (OR=3.78 [95% CI: 1.29, 4.78]), with the highest likelihood again found in men experiencing high levels of anxious-depressive symptoms (OR=5.00 [95% CI: 1.15, 8.23).

5.4 DISCUSSION

This population-based study of Norwegian adults demonstrates that symptoms of depression and anxiety are differentially associated with behavioural and clinical outcomes in individuals with Type 2 diabetes. Overall, we confirmed the high prevalence of anxious and depressive symptoms previously documented in individuals with Type 2 diabetes [28, 29]. We observed associations between these symptoms and diet adherence, the subjective diabetes experience, c-reactive protein levels, and glycemic control, and highlight several differences according to symptom type and sex below. Symptoms of depression and anxiety were not associated with the remaining clinical (i.e., waist girth, HDL cholesterol, and triglyceride levels) and behavioural (i.e., glucose monitoring and foot checks at home) outcomes in our study.

Interestingly, we observed that symptoms of depression alone were associated only with behavioural measures following adjustment for covariates. For example, depressed individuals were less likely to report avoiding saturated fats. Negative mood and fat consumption have been consistently linked throughout the literature, and high fat foods may be used by depressed individuals as a form of self-medication or attempt to balance neurotransmitters involved in the regulation of mood [30]. Contrary to this, women who experienced symptoms of anxiety (either alone or concurrently with symptoms of depression) reported being more likely to avoid high fat foods. This may be attributable to a tendency towards increased health seeking behaviour in anxious individuals [31], and previous studies show that females who are anxious about their health are more inclined to diet than non-anxious individuals [32]. This sex-specific pattern was also observed with respect to vegetable consumption (although it was not statistically significant). Women experiencing symptoms of depression or anxiety were more likely to report frequent vegetable consumption (regardless of symptom type), whereas men experiencing these symptoms reported a decreased odds of doing so. This may point to

phenotypic differences in affective symptoms experienced by men and women, an area in which little research has been done [33]. One study suggests that gender differences do exist across specific dimensions of health anxiety (i.e., , reassurance-seeking and worry), while core dimensions of this condition remain invariant across gender and generalize to both men and women [34]. Sex-specific differences in these phenotypic or dimensional presentations of depression and anxiety may be impactful, especially given the recent finding that while depression and anxiety appear to have long term effects on mortality in all individuals with Type 2 diabetes, these excess mortality rates associated with these symptoms are more pronounced in men than women [35].

We also observed a positive association between symptoms of anxiety and high serum CRP in women. Previous studies demonstrate a dose-response relationship between cumulative depressive episodes and subsequent c-reactive protein levels [26, 36], providing stronger evidence for a long-term pathway from depression to later CRP levels than from CRP to later depression [36]. This is important as inflammatory markers, such as c-reactive protein and other cytokines, have been linked to the pathogenesis of Type 2 diabetes and cardiovascular disease [37]. It is therefore biologically plausible that the risk for vascular complications in diabetic individuals could begin early and be governed by long-term emotional functioning [36]. However, none of these studies appear to have adjusted for the presence of anxiety. Although our results with respect to depressive symptoms demonstrated a similar direction of effect, these were lesser in magnitude and not statistically significant. In male participants, the direction of this effect appeared to be reversed (i.e., anxiety was associated with a reduced odds of high CRP levels), but was not statistically significant. Our findings therefore suggest that women with Type 2 diabetes experiencing high levels of anxiety may be at particular risk of the above processes occurring, although longitudinal research is needed to address the potential for reverse-causation with respect to these factors present in the current study.

Our third key finding reflected strong associations between symptoms of depression and anxiety and glycemic control in men only. Our study found that men experiencing symptoms of depression or concurrent depression-anxiety had over triple the odds of having high HbA1c (i.e., above 5.0% (31 mmol/mol)). In females, the opposite effects were observed (i.e., associated with reduced odds of high HbA1c), although not statistically significant. This is in line with previous research demonstrating a relationship between poor glycemic control and depressive symptoms in men, but not women [3]. Although inferences about temporality are not made possible in our study, there is evidence from multiple trials that psychological interventions for depression do lead to subsequent improvements in HbA1C levels [38]. Our findings suggest that these effects may not extend to symptoms of anxiety, and that it may be useful to examine whether such interventions would yield similar benefits in men and women.

We also observed several less novel findings related to behavioural outcomes. For example, both men and women with high levels of depressive or anxious symptoms were much more likely to report having a negative subjective experience of having Type 2 diabetes than those without, with over twice the odds of reporting that having diabetes is difficult or that dietary adherence is problematic. Research shows that the psychosocial aspect of diabetes may negatively impact health-related quality of life, which in turn may negatively influence diabetes self-management [39]. Previous research also demonstrates depression and anxiety to be independently associated with physical inactivity in high-risk cardiovascular patient populations [40], and the current study shows both affective symptom groups to be associated with physical inactivity. While exercise already occupies a prominent place in most diabetes counselling programs, the present study stresses the potential importance of addressing both anxious and depressive symptoms in order to break this cycle.

It has been postulated that symptoms of anxiety and depression fall along a single continuum of mental illness, representing the same neurobiological origin [41]. However, the present study indicates that these different symptom types may result in divergent effects on biological processes that are critical for chronic disease management. For example, the strong association observed between HbA1c and depressive or concurrent depressive-anxious symptoms in men may indicate that unique aspects of the depressive experience (e.g., lethargy or fat consumption) may play a role in glycemic control that are not present in relation to anxiety. Previous research suggests that the association between depressive symptoms and glycemic control may be specific to anhedonic symptoms, whereby anhedonia was found to be significantly associated with suboptimal glycemic control, but both depressed mood and anxiety were not [42]. It is also worth noting that many of the outcomes examined here may themselves be linked (e.g., physical inactivity and glycemic control). While depression and anxiety may not necessarily affect clinical outcomes directly, they may do so through related behavioural factors [43]. In the aforementioned study, alcohol consumption and physical activity met criteria for mediation, but did not attenuate the association between anhedonia and glycemic control by more than 5% [42]. It appears that additional research which examines the distinct features or symptom dimensions of depression and anxiety and their associations with diabetes outcomes would be particularly useful to further contextualize the results of the present study. Future scientific inquiry may also clarify these processes further by unpacking the contributions of mediating factors in these relationships, which may ultimately aid in tailoring individual Type 2 diabetes management and treatment strategies more effectively.

5.4.1 Strengths and Limitations

The major strength of this study was a design that allowed the examination of unique associations between three common affective symptom phenotypes and a range of diabetic

outcomes. In addition, we used high quality data on a large, population based sample, and rigorously controlled for a range of clinical and sociodemographic covariates.

However, our cross-sectional study design also precluded a discussion of temporality with respect to these relationships. Research based on this survey may also not easily generalize to other populations, as Nord-Trøndelag is a rural county which demonstrates little ethnic heterogeneity. In addition, we used a self-report scale to measure depression and anxiety rather than a diagnostic interview. Although high congruence has been demonstrated between these tools and diagnostic instruments [44], the CONOR-MHI has not yet been validated against a gold standard diagnostic interview. However, since depression and anxiety remain largely undiagnosed in community settings [45], the use of a self-report scale may have allowed us to capture individuals with clinically relevant symptoms falling below the threshold for either disorder [46]. Many of the symptoms of depression and anxiety reported in people with Type 2 diabetes may also be related to their diabetes (i.e., diabetes distress), rather than be representative of a comorbid psychopathology. Of concern is that mistaking diabetes-related distress for depression can lead to inappropriate psychiatric treatment [47]. However, as described in detail by Fisher et al. (2014), these overlapping affective states likely share an underlying common construct of emotional distress [47]. They further suggest that attempts to integrate treatment of emotional distress into regular diabetes care, specifically approaches which consider the diabetes context, may be widely beneficial to patients across a range of affective states. While we are not able to differentiate between overlapping constructs of depression, anxiety, and diabetes-related distress in the current study, we believe that such approaches to addressing emotional distress would benefit diabetes patients experiencing a range of depression and anxiety symptoms, such as those measured here.

As with all observational studies, these results are subject to the presence of unmeasured confounders, such as educational attainment (which was not measured in the HUNT 3 survey wave). Education may moderate the relationship between affective symptoms and specific diabetes outcomes, and based on previous literature [48] these estimates would likely be underestimated in those with low educational attainment and overestimated in those with high educational attainment. However, according to data from previous HUNT surveys, we expect that less than 10% of our current study population will have received a post-secondary education, and that overall our estimates would not change drastically. We were also unable to control for the effects of antidepressant or anxiolytic medication use which may have confounded these associations; some (e.g., fluoxetine) by reducing hyperglycemica and increasing insulin sensitivity, and others (e.g., desimaprine) by exerting opposite effects [49]. It is therefore difficult to judge from previous research what the net potential effect of this omission on our outcomes might be. In addition, the self-report nature of the behavioural questions provide a measure of what respondents believe their behaviors to be based on individual interpretations of these items, rather than providing an objective measure of these outcomes. Questions related to diet adherence, in particular, were not clearly defined the HUNT study. Future research using more rigorous objective assessments of diabetes management would help to validate these findings.

5.4.2 Conclusions

We provide evidence that symptoms of depression and anxiety are differential predictors of adverse Type 2 diabetes outcomes. We did not find that concurrent anxious-depressive symptoms were associated with notably higher odds of poor outcomes than either category alone, which suggests the importance of specific symptomatology rather than overall symptom load in these outcomes. We also found sex-related differences with respect to two important

clinical outcomes (i.e., anxiety and CRP in women and depression and glycemic control in men). Our study highlights some potentially valuable novel findings, and we therefore encourage any attempts at replication in order to substantiate their validity. These findings should alert practitioners to the importance of detection and management of symptoms of both anxiety and depression in Type 2 diabetes cases.

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We would like to acknowledge the Nord-Trøndelag residents who participated in the HUNT study. The Nord-Trøndelag Health Study (The HUNT Study) is a collaboration between HUNT Research Centre (Faculty of Medicine, Norwegian University of Science and Technology NTNU), Central Norway Regional Health Authority, Nord-Trøndelag County Council and The Norwegian Institute of Public Health.

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Table 5.1: Sociodemographic and health characteristics of HUNT 3 cohort members, by affective symptom status (N=2,035)

	Depressive Symptoms Only (n=258)	Anxious Symptoms Only (n=402)	Comorbid Depression-Anxiety (n=179)	No Affective Symptoms (n=1,196)
Age (mean, SD)	64.7 (14.6)	66.2 (9.7)	62.8 (11.7)	64.8 (11.5)
Sex (Female, %)	55.8%	54.3%	49.5%	45.5%
Marital status (married)	40.4%	60.6%	54.2%	66.3%
BMI (mean)	31.3 (4.3)	30.2 (5.1)	31.8 (4.6)	30.4 (4.9)
Waist girth in cm (mean)				
Men	107.9 (13.1)	106.9 (11.1)	107.7 (12.5)	104.6 (10.7)
Women	102.8 (13.2)	102.6 (12.8)	105.5 (11.6)	102.2 (13.1)
Physical Inactivity	25.4%	29.1%	27.8%	16.8%
Alcohol (drinks per week)	3.6 (5.5)	2.3 (4.0)	4.8 (7.9)	3.1 (4.9)
Smoking (pack-years, mean)	16.3 (10.8)	22.1 (14.7)	21.5 (17.2)	20.1 (15.6)
Smoking status (yes, current)	16.2%	22.0%	16.7%	13.1%
Family History (Yes)	16.3 (10.8)	22.1 (14.7)	21.5 (17.2)	20.1 (15.6)
Chronic Conditions (Yes)	65.8%	73.7%	73.3%	63.7%

Table 5.2: Odds ratios for clinical and behavioural outcomes measures in individuals with Type 2 diabetes, by anxious and depressive symptoms (N=2,035)

	Depressive Symptoms		Anxious Symptoms		Comorbid Anxious-Depressive Symptoms	
	Crude[a]	Adjusted[b]	Crude[a]	Adjusted[b]	Crude[a]	Adjusted[b]
Clinical Measures[c]						
Waist girth	1.29 [0.61, 2.74]	1.03 [0.46, 2.30]	1.09 [1.07, 4.06]	1.77 [0.87, 3.58]	1.90 [0.68, 5.32]	1.63 [0.54, 4.93]
HDL Cholesterol	1.04 [0.71, 1.50]	0.95 [0.62, 1.46]	1.01 [0.76, 1.34]	0.79 [0.57, 1.10]	1.04 [0.67, 1.62]	0.83 [0.51, 1.37]
Systolic BP	0.77 [0.58, 1.04]	0.81 [0.59, 1.11]	0.76 [0.57, 1.01]	**0.71 [0.52, 0.97]**	0.74 [0.48, 1.13]	0.74 [0.47, 1.16]
Triglycerides	1.27 [0.86, 1.89]	1.30 [0.83, 2.05]	1.21 [0.90, 1.63]	1.20 [0.85, 1.70]	1.17 [0.74, 1.86]	1.28 [0.75, 2.20]
Serum CRP	1.32 [0.99, 1.77]	1.33 [0.97, 1.81]	**1.53 [1.15, 2.03]**	1.20 [0.88, 1.64][d]	**1.68 [1.11, 2.54]**	1.41 [0.91, 2.20]
HbA1c	1.10 [0.68, 1.78]	1.20 [0.72, 2.01][d]	1.21 [0.84, 1.74]	1.19 [0.80, 1.77]	1.16 [0.67, 2.04]	1.40 [0.75, 2.60][d]
Random Serum Glucose	1.24 [0.80, 1.92]	1.20 [0.75, 1.91][d]	**1.83 [1.33, 2.53]**	**1.87 [1.32, 2.63]**	1.57 [0.96, 2.56]	1.63 [0.97, 2.73][d]
Self-Management Behaviours						
Diet Adherence						
Avoid saturated fats	**0.27 [0.09, 0.78]**	**0.20 [0.06, 0.68]**	1.09 [0.74, 1.61]	1.15 [0.77, 1.73][d]	0.99 [0.64, 1.51]	1.12 [0.72, 1.73]
Eat vegetables	1.56 [0.96, 2.53]	1.19 [0.48, 2.97]	1.48 [0.92, 2.40]	**1.66 [1.02, 2.73]**	1.24 [0.72, 2.12]	0.99 [0.54, 1.81]
Exercise *(< 2-3/week)*	**1.73 [1.43, 2.80]**	**1.69 [1.37, 2.72]**	**1.60 [1.12, 2.29]**	**1.57 [1.08, 2.27]**	**1.55 [1.01, 2.40]**	**1.55 [1.03, 2.44]**
Checks glucose at home	0.63 [0.21, 1.85]	0.61 [0.20, 1.81]	1.03 [0.63, 1.68]	1.09 [0.65, 1.81]	0.97 [0.50, 1.92]	1.12 [0.56, 2.23]
Checks feet at home	0.47 [0.18, 1.26]	0.51 [0.19, 1.36]	1.23 [0.80, 1.89]	1.15 [0.73, 1.81]	1.04 [0.60, 1.82]	0.99 [0.55, 1.78]
Diabetes Experience						
It is a problem can't eat what I want	1.81 [0.84, 3.93]	**2.60 [2.32, 4.00]**	**2.85 [1.86, 4.34]**	**2.66 [1.71, 4.16]**	**2.70 [1.57, 4.64]**	**2.26 [1.30, 3.95]**
Find that diabetes is difficult	**2.25 [1.06, 4.82]**	**2.41 [1.10, 4.30]**	**2.52 [1.68, 3.77]**	**2.56 [1.68, 3.91]**	**3.52 [1.46, 4.33]**	**3.26 [1.30, 3.92]**

Bold values indicate significance at p<0.05

[a]Adjusted for age and sex

[b]Adjusted for age, sex, waist circumference, family history of diabetes, marital status

[c] Additionally adjusted for all other clinical factors (waist girth, HDL cholesterol, systolic BP, triglycerides, CRP, and serum glucose)

[d] Indicates significant interaction by sex at p<0.05

Table 5.3: Adjusted odds ratios for clinical and self-management outcomes in women with Type 2 diabetes, by anxious and depressive symptoms* (n=961)

	Adjusted OR [95% CI]		
	Depressive Symptoms[a]	Anxious Symptoms[a]	Comorbid Anxious-Depressive Symptoms[a]
Clinical Measures[b]			
Waist girth	1.04 [0.95, 3.70]	1.60 [0.45, 5.73]	1.58 [0.20, 12.58]
HDL Cholesterol	1.14 [0.61, 2.13]	0.86 [0.54, 1.38]	0.86 [0.42, 1.79]
Systolic BP	0.81 [0.51, 1.30]	0.74 [0.49, 1.13]	0.85 [0.45, 1.58]
Triglycerides	0.15 [0.61, 2.17]	0.95 [0.58, 1.53]	1.12 [0.53, 2.37]
Serum CRP	1.21 [0.78, 1.87]	**1.57 [1.05, 2.34]**	1.35 [0.75, 2.42]
HbA1c	0.58 [0.28, 1.20]	0.97 [0.56, 1.68]	0.72 [0.31, 1.68]
Non-Fasting Serum Glucose	0.45 [0.17, 1.17]	1.66 [0.97, 2.84]	0.49 [0.17, 1.46]
Self-Management Behaviours			
Diet Adherence			
Avoid saturated fats	1.50 [0.88, 2.56]	**1.71 [1.17, 1.94]**	**2.08 [1.08, 4.00]**
Eat vegetables	1.48 [0.72, 3.05]	1.07 [0.53, 2.22]	1.68 [0.68, 4.16]
Exercise *(< 2-3 times/week)*	**1.42 [1.28, 1.58]**	**1.42 [1.30, 1.55]**	**1.48 [1.29, 1.69]**
Checks glucose at home	1.11 [0.66, 1.87]	1.18 [0.73, 1.90]	0.85 [0.40, 1.82]
Checks feet at home	1.18 [0.60, 2.29]	1.15 [0.68, 1.94]	1.46 [0.68, 3.15]
Diabetes Experience			
It is a problem I can't eat what I want	**2.17 [1.43, 3.27]**	**1.94 [1.24, 3.02]**	**3.32 [1.78, 6.17]**
Find that diabetes is difficult	**2.62 [1.64, 4.17]**	**2.54 [1.69, 3.82]**	**3.90 [2.00, 7.60]**

Bold values indicate significance at $p<0.05$

[a]Adjusted for age, sex, waist circumference, family history of diabetes, marital status

[b] Additionally adjusted for all other clinical factors (waist girth, HDL cholesterol, systolic BP, triglycerides, CRP, and serum glucose)

Table 5.4: Adjusted odds ratios for clinical and self-management outcomes in men with Type 2 diabetes, by anxious and depressive symptoms* (n=1,074)

	Adjusted OR [95% CI]		
	Depressive Symptoms[a]	Anxious Symptoms[a]	Comorbid Anxious-Depressive Symptoms[a]
Clinical Measures[b]			
Waist girth	1.17 [0.45, 3.00]	1.51 [0.70, 3.26]	1.32 [0.42, 4.17]
HDL Cholesterol	0.80 [0.44, 1.45]	0.75 [0.47, 1.19]	0.78 [0.39, 1.58]
Systolic BP	0.79 [0.51, 1.22]	0.63 [0.39, 1.01]	0.60 [0.31, 1.17]
Triglycerides	0.68 [0.38, 1.22]	0.83 [0.52, 1.31]	0.49 [0.25, 0.95]
Serum CRP	1.48 [0.95, 2.30]	0.85 [0.50, 1.45]	1.55 [0.78, 3.10]
HbA1c	**3.78 [1.29, 4.78]**	1.49 [0.80, 2.78]	**5.00 [1.15, 8.23]**
Non-Fasting Serum Glucose	**2.02 [1.12, 3.62]**	**1.97 [1.25, 3.10]**	**3.20 [1.64, 6.20]**
Self-Management Behaviours			
Diet Adherence			
Avoid saturated fats	1.40 [0.91, 2.15]	0.92 [0.56, 1.51]	0.87 [0.41, 1.85]
Eat vegetables	0.54 [0.22, 1.33]	0.81 [0.41, 1.58]	0.48 [0.14, 1.61]
Exercise *(< 2-3 times/week)*	**1.23 [1.08, 1.40]**	**1.19 [1.07, 1.32]**	**1.25 [1.06, 1.47]**
Checks glucose at home	0.55 [0.21, 1.46]	1.20 [0.65, 2.21]	0.99 [0.36, 2.70]
Checks feet at home	0.61 [0.28, 1.32]	1.17 [0.70, 1.97]	0.65 [0.26, 1.60]
Diabetes Experience			
It is a problem I can't eat what I want	**2.57 [1.60, 4.13]**	**2.00 [1.32, 3.04]**	**2.95 [1.43, 6.09]**
Find that diabetes is difficult	**2.39 [1.59, 3.60]**	**3.39 [2.08, 5.52]**	**3.02 [1.48, 6.16]**

Bold values indicate significance at $p<0.05$

[a]Adjusted for age, sex, waist circumference, family history of diabetes, marital status

[b] Additionally adjusted for all other clinical factors (waist girth, HDL cholesterol, systolic BP, triglycerides, CRP, and serum glucose)

REFERENCES

1. Golden SH, Shah N, Naqibuddin M, et al (2017) The Prevalence and Specificity of Depression Diagnosis in a Clinic-Based Population of Adults With Type 2 Diabetes Mellitus. Psychosomatics 58:28–37. doi: 10.1016/j.psym.2016.08.003

2. Semenkovich K, Brown ME, Svrakic DM, Lustman PJ (2015) Depression in type 2 diabetes mellitus: prevalence, impact, and treatment. Drugs 75:577–87. doi: 10.1007/s40265-015-0347-4

3. Cherrington A, Wallston KA, Rothman RL (2010) Exploring the relationship between diabetes self-efficacy, depressive symptoms, and glycemic control among men and women with type 2 diabetes. J Behav Med 33:81–9. doi: 10.1007/s10865-009-9233-4

4. Safren SA, Gonzalez JS, Wexler DJ, et al (2014) A randomized controlled trial of cognitive behavioral therapy for adherence and depression (CBT-AD) in patients with uncontrolled type 2 diabetes. Diabetes Care 37:625–33. doi: 10.2337/dc13-0816

5. de Wit LM, van Straten A, van Herten M, et al (2009) Depression and body mass index, a u-shaped association. BMC Public Health 9:14. doi: 10.1186/1471-2458-9-14

6. Black S, Markides K, Ray L (2003) Depression predicts increased incidence of adverse health outcomes in older Mexican Americans with type 2 diabetes. Diabetes Care

7. Lin EHB, Rutter CM, Katon W, et al (2010) Depression and advanced complications of diabetes: a prospective cohort study. Diabetes Care 33:264–9. doi: 10.2337/dc09-1068

8. Lin E, Katon W, Korff M Von (2004) Relationship of depression and diabetes self-care, medication adherence, and preventive care. Diabetes Care 27:

9. Gale CR, Kivimaki M, Lawlor DA, et al (2010) Fasting Glucose, Diagnosis of Type 2 Diabetes, and Depression: The Vietnam Experience Study. Biol Psychiatry 67:189–192. doi: 10.1016/j.biopsych.2009.09.019

10. Nichols GA, Moler EJ (2011) Cardiovascular disease, heart failure, chronic kidney disease and depression independently increase the risk of incident diabetes. Diabetologia 54:523–526. doi: 10.1007/s00125-010-1965-8

11. Demakakos P, Pierce MB, Hardy R (2010) Depressive symptoms and risk of type 2 diabetes in a national sample of middle-aged and older adults: the English longitudinal study of aging. Diabetes Care 33:792–7. doi: 10.2337/dc09-1663

12. Demakakos P, Zaninotto P, Nouwen A (2014) Is the association between depressive symptoms and glucose metabolism bidirectional? Evidence from the English Longitudinal Study of Ageing. Psychosom Med 76:555–61. doi: 10.1097/PSY.0000000000000082

13. Baldwin D, Rudge S (1995) The role of serotonin in depression and anxiety. Int Clin Psychopharmacol 9 Suppl 4:41–5.

14. Gelenberg AJ (2000) Psychiatric and Somatic Markers of Anxiety: Identification and Pharmacologic Treatment. Prim Care Companion J Clin Psychiatry 2:49–54.

15. Zbozinek TD, Rose RD, Wolitzky-Taylor KB, et al (2012) Diagnostic overlap of generalized anxiety disorder and major depressive disorder in a primary care sample. Depress Anxiety 29:1065–71. doi: 10.1002/da.22026

16. Vogelzangs N, Beekman ATF, de Jonge P, Penninx BWJH (2013) Anxiety disorders and inflammation in a large adult cohort. Transl Psychiatry 3:e249. doi: 10.1038/tp.2013.27

17. Anderson RJ, Grigsby AB, Freedland KE, et al (2002) Anxiety and Poor Glycemic Control: A Meta-Analytic Review of the Literature. Int J Psychiatry Med 32:235–247. doi: 10.2190/KLGD-4H8D-4RYL-TWQ8

18. Hofmeijer-Sevink MK, Batelaan NM, van Megen HJGM, et al (2012) Clinical relevance of comorbidity in anxiety disorders: a report from the Netherlands Study of Depression and Anxiety (NESDA). J Affect Disord 137:106–12. doi: 10.1016/j.jad.2011.12.008

19. Brintzenhofe-Szoc KM, Levin TT, Li Y, et al (2009) Mixed anxiety/depression symptoms in a large cancer cohort: prevalence by cancer type. Psychosomatics 50:383–91. doi: 10.1176/appi.psy.50.4.383

20. Krokstad S, Langhammer A, Hveem K, et al (2013) Cohort Profile: the HUNT Study, Norway. Int J Epidemiol 42:968–77. doi: 10.1093/ije/dys095

21. Langhammer A, Krokstad S, Romundstad P, et al (2012) The HUNT study: participation is associated with survival and depends on socioeconomic status, diseases and symptoms. BMC Med Res Methodol 12:143. doi: 10.1186/1471-2288-12-143

22. Søgaard A, Bjelland I, Tell G, Røysamb E (2003) A comparison of the CONOR Mental Health Index to the HSCL-10 and HADS. Nor. Epidemiol.

23. Alberti KGMM, Zimmet P, Shaw J (2006) Metabolic syndrome-a new world-wide definition. A Consensus Statement from the International Diabetes Federation. Diabet Med 23:469–480. doi: 10.1111/j.1464-5491.2006.01858.x

24. Bhattacharyya OK, Estey EA, Cheng AYY (2008) 2008 clinical practice guidelines for the prevention and management of diabetes in Canada.

25. Pearson TA, Mensah GA, Alexander RW, et al (2003) Markers of Inflammation and Cardiovascular Disease. Circulation 107:

26. Howren MB, Lamkin DM, Suls J (2009) Associations of Depression With C-Reactive Protein, IL-1, and IL-6: A Meta-Analysis. Psychosom Med 71:171–186. doi: 10.1097/PSY.0b013e3181907c1b

27. Royston P (2004) Multiple Imputation of Missing Values. The Stata Journal, 4 (3), 227–241.

28. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ (2001) The Prevalence of Comorbid Depression in Adults With Diabetes: A meta-analysis. Diabetes Care 24:1069–1078. doi: 10.2337/diacare.24.6.1069

29. Grigsby AB, Anderson RJ, Freedland KE, et al (2002) Prevalence of anxiety in adults with diabetes: a systematic review. J Psychosom Res 53:1053–60.

30. Bruinsma K, Taren DL, Rudin R., et al (1999) Chocolate: Food or Drug? J Am Diet Assoc 99:1249–1256. doi: 10.1016/S0002-8223(99)00307-7

31. Hu WHC, Wong W-M, Lam CLK, et al (2002) Anxiety but not depression determines health care-seeking behaviour in Chinese patients with dyspepsia and irritable bowel syndrome: a population-based study. Aliment Pharmacol Ther 16:2081–2088. doi: 10.1046/j.1365-2036.2002.01377.x

32. Hadjistavropoulos H, Lawrence B (2007) Does anxiety about health influence eating patterns and shape-related body checking among females? Pers Individ Dif 43:319–328. doi: 10.1016/j.paid.2006.11.021

33. Kornstein S., Schatzberg A., Thase M., et al (2000) Gender differences in chronic major and double depression. J Affect Disord 60:1–11. doi: 10.1016/S0165-0327(99)00158-5

34. MacSwain KLH, Sherry SB, Stewart SH, et al (2009) Gender differences in health anxiety: An investigation of the interpersonal model of health anxiety. Pers Individ Dif 47:938–943. doi: 10.1016/j.paid.2009.07.020

35. Naicker K, Johnson JA, Skogen JC, et al (2017) Type 2 Diabetes and Comorbid Symptoms of

Depression and Anxiety: Longitudinal Associations With Mortality Risk. Diabetes Care

36. Copeland WE, Shanahan L, Worthman C, et al (2012) Cumulative Depression Episodes Predict Later C-Reactive Protein Levels: A Prospective Analysis. Biol Psychiatry 71:15–21. doi: 10.1016/j.biopsych.2011.09.023

37. Donath MY, Shoelson SE (2011) Type 2 diabetes as an inflammatory disease. Nat Rev Immunol 11:98–107. doi: 10.1038/nri2925

38. Ismail K, Winkley K, Rabe-Hesketh S, et al (2004) Systematic review and meta-analysis of randomised controlled trials of psychological interventions to improve glycaemic control in patients with type 2 diabetes. Lancet (London, England) 363:1589–97. doi: 10.1016/S0140-6736(04)16202-8

39. Polonsky WH (2002) Emotional and quality-of-life aspects of diabetes management. Curr Diab Rep 2:153–159. doi: 10.1007/s11892-002-0075-5

40. Bonnet F, Irving K, Terra J-L, et al (2005) Anxiety and depression are associated with unhealthy lifestyle in patients at risk of cardiovascular disease. Atherosclerosis 178:339–44. doi: 10.1016/j.atherosclerosis.2004.08.035

41. Baldwin DS, Evans DL, Hirschfeld RMA, Kasper S (2002) Can we distinguish anxiety from depression? Psychopharmacol Bull 36 Suppl 2:158–65.

42. Nefs G, Pouwer F, Denollet J, et al (2012) Suboptimal glycemic control in type 2 diabetes: a key role for anhedonia? J Psychiatr Res 46:549–54. doi: 10.1016/j.jpsychires.2012.01.013

43. Carter J, Swardfager W (2016) Mood and metabolism: Anhedonia as a clinical target in Type 2 diabetes. Psychoneuroendocrinology 69:123–132. doi: 10.1016/j.psyneuen.2016.04.002

44. Lundin A, Hallgren M, Forsell Y (2015) The validity of the symptom checklist depression and anxiety subscales: A general population study in Sweden. J Affect Disord 183:247–252. doi: 10.1016/j.jad.2015.05.024

45. Masmoudi J, Damak R, Zouari H, et al (2013) Prevalence and Impact of Anxiety and Depression on Type 2 Diabetes in Tunisian Patients over Sixty Years Old. Depress Res Treat 2013:341782. doi: 10.1155/2013/341782

46. Hybels CF, Blazer DG, Pieper CF (2001) Toward a Threshold for Subthreshold Depression: An Analysis of Correlates of Depression by Severity of Symptoms Using Data From an Elderly Community Sample. Gerontologist 41:357–365. doi: 10.1093/geront/41.3.357

47. Fisher L, Gonzalez JS, Polonsky WH (2014) The confusing tale of depression and distress in patients with diabetes: a call for greater clarity and precision. Diabet Med 31:764–72. doi: 10.1111/dme.12428

48. Carnethon MR, Kinder LS, Fair JM, et al (2003) Symptoms of Depression as a Risk Factor for Incident Diabetes: Findings from the National Health and Nutrition Examination Epidemiologic Follow-up Study, 1971-1992. Am J Epidemiol 158:416–423. doi: 10.1093/aje/kwg172

49. McIntyre RS, Soczynska JK, Konarski JZ, Kennedy SH (2006) The effect of antidepressants on glucose homeostasis and insulin sensitivity: synthesis and mechanisms. Expert Opin Drug Saf 5:157–168. doi: 10.1517/14740338.5.1.157

Appendix 5A. Sensitivity analysis comparing imputed and unimputed adjusted odds ratios for clinical and behavioural outcome measures in individuals with Type 2 diabetes[a]

	Depressive Symptoms		Anxious Symptoms		Comorbid Anxious-Depressive Symptoms	
	Non-Imputed[c]	Imputed	Non-Imputed[c]	Imputed	Non-Imputed[c]	Imputed
Clinical Measures[b]						
Waist girth	1.61 [0.75, 3.49]	1.03 [0.46, 2.30]	1.96 [1.05, 3.66]	1.77 [0.87, 3.58]	2.32 [0.80, 6.69]	1.63 [0.54, 4.93]
HDL Cholesterol	0.94 [0.63, 1.39]	0.95 [0.62, 1.46]	0.97 [0.78, 1.46]	0.79 [0.57, 1.10]	0.90 [0.56, 1.44]	0.83 [0.51, 1.37]
Systolic BP	0.81 [0.56, 1.17]	0.81 [0.59, 1.11]	0.83 [0.62, 1.10]	**0.71 [0.52, 0.97]**	0.74 [0.48, 1.13]	0.74 [0.47, 1.16]
Triglycerides	1.27 [0.86, 1.89]	1.30 [0.83, 2.05]	1.03 [0.76, 1.38]	1.20 [0.85, 1.70]	1.14 [0.72, 1.80]	1.28 [0.75, 2.20]
Serum CRP	1.32 [0.91, 1.89]	1.33 [0.97, 1.81]	1.31 [0.98, 1.74]	1.20 [0.88, 1.64]	1.45 [0.94, 2.22]	1.41 [0.91, 2.20]
HbA1c	1.21 [0.72, 1.76]	1.20 [0.72, 2.01]	1.14 [0.84, 1.56]	1.19 [0.80, 1.77]	1.19 [0.72, 1.97]	1.40 [0.75, 2.60]
Random Serum Glucose	1.19 [0.78, 1.82]	1.20 [0.75, 1.91]	**1.37 [1.12, 1.89]**	**1.87 [1.32, 2.63]**	1.47 [0.92, 2.36]	1.63 [0.97, 2.73]
Diet Adherence						
Avoid saturated fats	**0.44 [0.20, 0.81]**	**0.20 [0.06, 0.68]**	0.99 [0.75, 1.31]	1.15 [0.77, 1.73]	0.90 [0.62, 1.30]	1.12 [0.72, 1.73]
Eat vegetables	1.15 [0.77, 1.75]	1.19 [0.48, 2.97]	**1.20 [1.03, 1.74]**	**1.66 [1.02, 2.73]**	1.15 [0.70, 1.89]	0.99 [0.54, 1.81]
Exercise *(< 2-3/week)*	**1.60 [1.12, 2.28]**	**1.69 [1.37, 2.72]**	**1.56 [1.18, 2.07]**	**1.57 [1.08, 2.27]**	**1.62 [1.07, 2.47]**	**1.55 [1.03, 2.44]**
Checks glucose at home	0.89 [0.51, 1.56]	0.61 [0.20, 1.81]	0.98 [0.67, 1.44]	1.09 [0.65, 1.81]	0.89 [0.45, 1.75]	1.12 [0.56, 2.23]
Checks feet at home	0.88 [0.55, 1.40]	0.51 [0.19, 1.36]	1.16 [0.80, 1.67]	1.15 [0.73, 1.81]	1.01 [0.60, 1.70]	0.99 [0.55, 1.78]
Diabetes Experience						
It is a problem can't eat what I want	**2.91 [2.25, 3.93]**	**2.60 [2.32, 4.00]**	**2.41 [1.76, 3.30]**	**2.66 [1.71, 4.16]**	**2.20 [1.32, 3.68]**	**2.26 [1.30, 3.95]**
Find that diabetes is difficult	**2.46 [1.62, 3.72]**	**2.41 [1.10, 4.30]**	**2.54 [1.87, 3.47]**	**2.56 [1.68, 3.91]**	**2.59 [1.58, 4.25]**	**3.26 [1.30, 3.92]**

Bold values indicate significance at $p<0.05$

[a]Adjusted for age, sex, waist circumference, family history of diabetes, marital status

[b] Additionally adjusted for all other clinical factors (waist girth, HDL cholesterol, systolic BP, triglycerides, CRP, and serum glucose)

[c] Refers to results from a complete-case analyses

Appendix 5B. STROBE Statement

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	122
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	123
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	124-125
Objectives	3	State specific objectives, including any prespecified hypotheses	125
Methods			
Study design	4	Present key elements of study design early in the paper	126
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	126
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	126
			127-129
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	127-129
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	130
Bias	9	Describe any efforts to address potential sources of bias	126
Study size	10	Explain how the study size was arrived at	130-131
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	130-131
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	130-131
		(*b*) Describe any methods used to examine subgroups and interactions	130
		(*c*) Explain how missing data were addressed	130
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	148
		(*e*) Describe any sensitivity analyses	122

Appendix 5B. STROBE Statement (continued)

Results			**Page**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	126, 132
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	132, 141
		(b) Indicate number of participants with missing data for each variable of interest	85
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	132
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	132, 142
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	132
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	142-144, 148
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	137-139
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	139-140
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	138
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	126, 132

Appendix 5C. Screenshot of letter confirming acceptance from *Psychoneuroendocrinology*

Tue 7/4, 6:38 PM
Kiyuri Naicker;
rosemarie.bluthe31@orange.fr
Inbox

You forwarded this message on 7/4/2017 7:14 PM

Ref: PNEC_2017_237_R1

Title: Symptoms of Anxiety and Depression in Type 2 Diabetes: Associations with Clinical Diabetes Measures and Self-Management Outcomes in the Norwegian HUNT Study

Journal: Psychoneuroendocrinology

Dear Dr. Naicker,

I am pleased to inform you that your paper has been accepted for publication. My own comments as well as any reviewer comments are appended to the end of this letter. Now that your manuscript has been accepted for publication it will proceed to copy-editing and production.

Thank you for submitting your work to Psychoneuroendocrinology. We hope you consider us again for future submissions.

Kind regards,

Robert Dantzer
Editor-in-Chief
Psychoneuroendocrinology

Appendix 5D. Ethical approval from HUNT Study committee for manuscript publication

NTNU

Fakultet for medisin og helsevitenskap
Institutt for samfunnsmedisin og sykepleie

Vår dato 26.05.2017 | Vår referanse 2014/22653/TRS
Deres dato | Deres referanse

Børge Sivertsen
Avdeling for helsefremmende arbeid
Nasjonalt folkehelseinstitutt
Boks 4404 Nydalen
0403 Oslo

HUNT publikasjonsutvalg

Manus: *Symptoms of anxiety and depression in type 2 diabetes: Associations with clinical diabetes measures and self-management outcomes in the Norwegian HUNT Study*
Forfattere: *Naicker K, Øverland S, Johnson JA, Manuel D, Skogen JC, Siversen B, Colman I*
Datert: *230517*

Publikasjonsutvalget har vurdert manuset ut fra den inngåtte avtalen om analyserettigheter til HUNT-data og retningslinjene for forvaltning og bruk av data, og har ingen innvendinger til at manuset publiseres slik det er fremlagt.

Publikasjonsutvalget ønsker kopi av artikkelen så snart den foreligger.

Med hilsen

Turid Rygg Stene
rådgiver

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CHAPTER 6:

TYPE 2 DIABETES AND SYMPTOMS OF DEPRESSION AND ANXIETY: LONGITUDINAL ASSOCIATIONS WITH MORTALITY RISK

Preface

The purpose of the study presented in this chapter was to estimate the excess mortality risk associated with Type 2 diabetes comorbid with depressive and anxious symptoms over the long term. This study tests the following hypotheses: 1) that mortality risk would be highest in individuals experiencing symptoms of concurrent depression-anxiety than either disorder alone, and 2) that these risks would be higher in men than in women.

The article presented in this chapter was published in *Diabetes Care* in March 2017, and is cited as: Naicker, K., Johnson, J. A., Skogen, J. C., Manuel, D., Øverland, S., Sivertsen, B., & Colman, I. (2017). Type 2 Diabetes and Comorbid Symptoms of Depression and Anxiety: Longitudinal Associations with Mortality Risk. *Diabetes Care*, *40*(3), 352-358 (see Appendix 6B for journal acceptance letter). All tables and figures are marked as primary and supplementary corresponding to the submitted version. Additional supporting documents, including sensitivity analyses and ethical approval, are included in appendices at the end of this chapter.

Contribution Statement: I was responsible for generating the study hypothesis and design, with guidance from supervisors and co-authors. I conducted the necessary statistical analysis, created all of the tables and figures, and drafted the final manuscript. I also responded to all comments arising from the peer review process.

ABSTRACT

Background/Objective: Depression is strongly linked to increased mortality in individuals with Type 2 diabetes. Despite high rates of co-occurring anxiety and depression, the risk of death associated with anxiety in individuals with Type 2 diabetes is poorly understood. The aim of this study was to document the excess mortality risk associated with symptoms of depression and/or anxiety comorbid with Type 2 diabetes at baseline, in a general population sample.

Research Design and Methods: Using data on 64 177 Norwegian adults from the Nord-Trøndelag Health Study (HUNT 2), with linkage to the Norwegian Causes of Death Registry, we assessed all-cause mortality from survey participation in 1995 through to 2013. We used Cox proportional hazards models to examine mortality risk over 18 years associated with Type 2 diabetes status and the presence of comorbid affective symptoms at baseline.

Results: Three clear patterns emerged from our findings. First, mortality risk in individuals with diabetes increased in the presence of either depression, anxiety, or both. Second, mortality risk was lowest for symptoms of anxiety, higher for concurrent depression-anxiety, and highest for depression. Third, excess mortality risk associated with depression and anxiety was observed in men with diabetes but not in women. The highest risk of death was observed in men with diabetes and symptoms of depression only (hazard ratio: 3.47, 95% confidence interval: 1.96, 6.14).

Conclusion/Interpretation: This study provides evidence that symptoms of anxiety affect mortality risk in individuals with Type 2 diabetes independently of symptoms of depression, in addition to attenuating the relationship between depressive symptoms and mortality in these individuals.

6.1 INTRODUCTION

Type 2 diabetes and depression are two leading global causes of morbidity and mortality, with Type 2 diabetes currently affecting over 9% and depression affecting 5% of the world's population in any given year (1,2). One out of four patients with Type 2 diabetes experiences a clinically significant form of depression, at a prevalence two to five times higher than observed in the general population (3). Major depression is a condition that routinely presents concurrent with symptoms of anxiety - between 50% and 75% of individuals diagnosed with major depression in primary care settings are also diagnosed with an anxiety disorder (4). These disorders share many documented similarities, including hypothalamic-pituitary-adrenal (HPA) axis dysregulation, activation of inflammatory responses, and impacts on functional impairment. Unsurprisingly, depressed patients with concurrent anxiety have a poorer prognosis, with higher severity, greater chronicity, and longer time spent in treatment (5).

Mortality studies of the general population have demonstrated a consistent association between depressive disorders and excess mortality (6). However, evidence for the relationship between anxiety disorders and mortality risk remains inconsistent. Some studies demonstrate a higher observed short-term risk of death, which dissipates over the long term (7). Other studies find that high levels of anxious symptoms are associated with reduced accidental mortality in early life, but higher non-accidental mortality in later life (8,9). A recent meta-analysis reflects a higher relative risk of mortality associated with depression than anxiety in the general population (10). Additional evidence suggests that the mortality risk associated with depression may differ according to sex (11–13), as well as disorder severity (14). For example, major depression is shown to increase

mortality risk in both men and women, while minor depression is associated with an increased risk only in men (14). With respect to anxiety disorders, excess mortality has been associated with anxiety disorders in men, but not women within the same study (15). However, as the presence of concurrent anxiety is rarely considered in depression research studies (or vice versa), the ability to attribute risk to either disorder is obscured.

Individuals with diabetes may be particularly vulnerable to the deleterious effects of affective symptoms. Depression is a known risk factor for noncompliance with medical treatment (16); this can be particularly problematic for a condition like Type 2 diabetes, which requires a high degree of patient self-management. Depression is often much less likely to be identified by medical practitioners in male patients (17), and may affect glycemic control more strongly in men than in women (18). Likewise, studies link anxiety disorders to heightened inflammation in men, but not women (19). Sex differences in mortality risk associated with affective disorders may therefore be even more pronounced in individuals with Type 2 diabetes than in the general population. Relatively little is known about the effect of comorbid anxiety on mortality risk in individuals with diabetes. The purpose of this study was to document the excess mortality risk associated with Type 2 diabetes and comorbid symptoms of depression and anxiety in a large general population sample, and determine whether men and women are differentially affected by this association.

6.2 METHODS

6.2.1 Data Sources and Study Sample

This study used data from the second wave of the Norwegian Nord-Trøndelag Health Study (HUNT 2). The HUNT study is a large population-based survey conducted over three waves, in 1984/86 (HUNT 1), 1995/97 (HUNT 2) and 2006/08 (HUNT 3). The survey was conducted using a simple non-stratified design that included every resident of the Nord-Trøndelag County over 20 years old. The study was primarily established to address arterial hypertension, diabetes, tuberculosis screening and quality of life (20), and the scope has since been expanded to include a wide range of somatic and mental illnesses, lifestyle and health determinants. The HUNT cohort profile and methodology has been well-described elsewhere (20). For the HUNT 2 wave, 92 100 individuals aged 20 to 89 years received an initial questionnaire and a personal invitation to participate. Of these, 65 648 (71%) attended a physical examination, where they also received a second questionnaire. As our study comparison consisted of individuals with or without Type 2 diabetes, individuals with Type 1 or other subtypes of diabetes (e.g. gestational or latent autoimmune diabetes of adults (LADA)) were excluded. All remaining HUNT 2 participants were included, consisting of 64 177 individuals.

6.2.2 Primary Outcome

Our primary outcome of interest was all-cause mortality. These data were obtained through linkage to the Norwegian Causes of Death Registry, for each year from 1995 through to 2013. This registry

is maintained by the Norwegian Institute of Public Health and includes information on cause of death for all deceased persons registered as residents in Norway at the time of death (21).

6.2.3 Exposure Variables

Our primary exposures were Type 2 diabetes status, depressive symptom level, and anxious symptom level. Individuals who self-reported Type 2 diabetes in the HUNT 2 study questionnaire or who had non-fasting plasma glucose levels >=7 received further clinical confirmation of diabetes status, based on results of three repeated laboratory tests (fasting plasma glucose, oral glucose tolerance, and serum HbA1c levels). In order to receive a final classification of Type 2 diabetes, all individuals were additionally confirmed to be anti-glutamic acid decarboxylase (anti-GAD) and anti-insulinoma-associated (anti-IA-2) negative (to exclude LADA cases), and confirmed as having not begun insulin treatment within one year of diagnosis.

Symptoms of depression and anxiety were measured in HUNT using a 7-item Mental Health Index (CONOR-MHI). This tool was derived from widely validated items from the General Health Questionnaire and the Hopkin's Symptoms Checklist (HSCL). It was further evaluated against both the HSCL-10 and Hospital Anxiety and Depression Scales (HADS), and found to have excellent accuracy when tested against each of these scales as a gold standard (AUC=0.902 and AUC=0.909, respectively) (22) . The internal consistency of the CONOR-MHI was also high (Cronbach alpha ≥0.80) across multiple Norwegian datasets (22). Individuals were classified as having "high" symptom levels if their mean scores on the depression items or anxiety items respectively were above the recommended cut-off of 2.15 (22). Individuals falling below this score were classified as having "low or no" affective symptoms.

In order to compare independent categories of depression, anxiety, and Type 2 diabetes status against our referent group of no diabetes and no affective symptoms, three variables were generated. The first contained levels of exposure to depressive symptoms and Type 2 diabetes status; the second, exposure to anxious symptoms and Type 2 diabetes status; and the third, exposure to concurrent depressive-anxious symptoms and Type 2 diabetes status. These variables were mutually exclusive (i.e. the depression-only model excluded individuals who had high anxiety scores, and vice versa). Respective models are illustrated in Supplementary Figure 1.

6.2.4 Other Variables

Covariates included age, education, waist circumference, physical activity, smoking, family history of diabetes, antidepressant use, insulin use, and comorbid chronic conditions. Age was included as a continuous variable. Education was classified as having completed any education beyond upper secondary school versus no higher education. Waist circumference was chosen over body mass index (BMI), due to its demonstrated clinical significance in predicting mortality risk beyond BMI (23), and was classified as high if it exceeded 94 cm for men or 79 cm for women. Individuals were classified as physically inactive if they fell below the cut-off of ≥150 minutes of moderate or ≥60 minutes of vigorous physical activity per week. Insulin and antidepressant use were reported if taken daily or almost daily within the previous 12 months. Individuals were included in the model as either non-smokers, former smokers, or current smokers, as both current and former smoking have known associations with affective symptoms, diabetes status and mortality risk (24–26). The presence of any additional chronic condition was included as a binary variable. This included all cancers, cardiac angina, asthma, epilepsy, or any thyroid disease.

Alcohol use was not included as a covariate, due to its irregular associations with cardiovascular mortality (i.e. it is protective at low levels but acts as a risk factor at high amounts) (27). All exposures and covariates were measured at baseline in 1995/97.

6.2.5 Statistical Analysis

Cox proportional hazards regression was used to model the risk of dying over the follow-up period associated with each baseline exposure category against the referent unexposed group. Univariate Cox regression was first used to assess the association between exposures and failure time, reported as hazard ratios (HRs). Multivariate Cox regression was then performed using imputation of missing covariate values, under the multiple imputation by chained equations (MICE) method. This technique created 30 imputed datasets, from which reported estimates were computed. The amount of data missing was low on almost all covariates.

A test of proportionality indicated no evidence to contradict the proportional hazards assumption in our model variables ($p>0.05$), and the global fit of the model also indicated a rejection of the null hypothesis ($p=0.08$) (28). Additional inspection of covariate-adjusted log-log plots for each exposure category indicated no deviations from parallel curves, and thus no violation of the proportional hazards assumption. Due to the simple sampling design of the HUNT survey, analytic weights were not recommended nor used. The functional form of the age covariate was specified using restricted cubic splines (as per Harrell's method), to account for the non-linear relationship between age and mortality (29). All final statistical models were either adjusted for or stratified by sex. STATA 14 was used for all analysis.

6.3 RESULTS

The response rate for HUNT 2 was 69.5%. Of our 64 177 participants, 1133 had Type 2 diabetes. Differences were observed at baseline between individuals with and without diabetes on most key covariates, specifically: age, education, waist circumference, physical activity, smoking, medication use, family history of diabetes, and comorbid chronic conditions (Table 6.1). The sex distribution was roughly equal in each group.

A total of 13 881 deaths occurred in individuals without diabetes, representing 20.82% of this group. A total of 754 deaths occurred in individuals with diabetes over the 18-year study period, representing over two thirds of this group. All key covariates listed above were strong predictors of mortality, and were included in the adjusted models. When compared with the 'no diabetes/no affective symptom' referent group, the adjusted risk of death was lowest for baseline symptoms of anxiety only, higher for baseline diabetes only, and highest for anxious symptoms comorbid with diabetes (HR=1.20 [95% CI: 1.11, 1.30], 1.44 [95% CI: 1.26, 1.65], and 1.66 [95% CI: 1.25, 2.19], respectively) (Table 6.2, Figure 6.1). Hazard ratios for the depression exposure followed the same pattern, with slightly larger observed effects (HR= 1.27 [95% CI: 1.14, 1.41], 1.50 [95% CI: 1.32, 1.70], and 2.10 [95% CI: 1.41, 3.13], respectively). In the concurrent anxious-depressive exposure, the same pattern was again observed (HR=1.22 [95% CI: 1.07, 1.40], 1.44 [95% CI: 1.29, 1.60], and 2.01 [95% CI: 1.18, 3.00], respectively).

Moderate differences were observed between men and women (Table 6.2). Specifically, compared to our referent group, the mortality risk in men with diabetes increased in the presence of comorbid depression (HR=3.47 [95% CI: 1.96, 6.14]) and depression-anxiety (HR=3.42 [95% CI: 1.84,

6.38]), and to a lesser extent comorbid anxiety (HR=2.14 [95% CI: 1.41, 3.27]). Compared to having diabetes alone, mortality risk in women increased in the presence of depression (HR=1.86 [95% CI: 1.53, 2.26] versus HR=2.05 [95% CI: 1.22, 2.72]), but was lowered in the presence of symptoms of anxiety (HR=1.38 [95% CI: 0.95, 2.01]) and concurrent depression-anxiety (HR=1.14 [95% CI: 0.57, 2.29]).

These sex differences were more pronounced in the diabetes subsample, where the presence of all affective symptom types were associated with statistically significant increases in mortality risk in men (see Table 6.3), but not in women (i.e., all confidence intervals included 1). The same overall pattern was also noted in the diabetes subsample, with excess mortality risk observed to be highest in the presence of depressive symptoms (HR=1.67 [95% CI: 1.18, 2.36]), slightly lower in the presence of concurrent depression-anxiety (HR=1.58 [95% CI: 1.16, 2.15), and nonsignificant in the presence of symptoms of anxiety (HR=1.30 [95% CI: 0.99, 1.69]) (Table 3).

6.4 DISCUSSION

Three clear patterns emerged from this large, population-based study of mortality risk associated with Type 2 diabetes and comorbid symptoms of depression and anxiety. First, mortality risk was lowest for affective symptoms alone, higher for diabetes alone, and highest for both combined. Second, excess mortality among those with diabetes was observed to be lowest for anxiety alone, higher for concurrent depression and anxiety, and highest for depression alone. Third, the effects of mental health symptoms appeared to be stronger in men with diabetes than in women. Overall, the highest risk of death was observed in men with diabetes and comorbid symptoms of depression alone.

The first pattern above illustrates the well-documented impact of mental health comorbidities on chronic disease outcomes. Findings from the WHO World Health Surveys, containing data from over 60 countries, conclude that the presence of comorbid depression incrementally worsens health more than any other combination of chronic diseases (30). Individuals suffering both chronic medical illness and co-morbid depression or anxiety have significantly higher health-care utilization, functional disability, and work absence than those without (31). Comorbid affective symptoms may magnify the impact of chronic illness through both biological and behavioural mechanisms, including innate immunity and inflammatory processes (e.g., proinflammatory cytokines and C-reactive protein), as well as physical inactivity or social adversity (32). The cognitive burden of diabetes is also suggested to increase low mood and negative thoughts, leading to worse diabetes self-care (33).

The second finding demonstrates different patterns of risk for symptoms of depression and anxiety. Overall, individuals with diabetes and depression had a 110% increased risk of death, compared to a 66% increased risk of death associated with symptoms of anxiety. It is worth noting that symptoms of anxiety alone were associated with increased mortality risk over the long term, regardless of diabetes status. Despite this, concurrent symptoms of depression-anxiety were not demonstrably more predictive of mortality than depression overall. This finding is supported by literature demonstrating a potentially protective effect of anxiety on mortality risk in the general population (34), and evidence that anxiety can be an independent predictor of health-seeking behaviours (35). The effects of comorbid anxiety on mortality risk may also explain why other research, such as three recent meta-analyses of prospective studies on depression as a risk factor for mortality in diabetes, report lower effect sizes for depression than those observed here (i.e., adjusted HRs of 1.49, 1.50, and 1.76, respectively) (36–38). Few studies account for potentially confounding symptoms of anxiety when quantifying the impact of depression on health outcomes, which may frequently bias these observed effects downward.

Our third finding highlights the differential associations between affective symptoms and mortality in men and women. Notably, while mood disorders are more common in women, affective symptoms in conjunction with diabetes yielded a significant increase in mortality risk only men. These findings are particularly illuminating given the lack of sex-specific results in most studies on mortality and diabetes. A range of patient and health care provider characteristics may affect these outcomes. As mentioned previously, men are less likely to be diagnosed or treated for depression (17), and may also experience greater increases in inflammatory agents in the presence of an anxiety disorder (e.g., C-reactive protein (19)). Another explanation could be that men

experience anxiety phenotypes associated with higher functional impairment than women. While sex differences in the prevalence of affective disorders are well documented, few studies to date have examined sex differences in the clinical features of anxiety or depression.

Despite the large body of evidence supporting links between depression and both mortality and diabetes, it is not possible to draw a causal conclusion from these findings for several reasons. Many of the risk factors for Type 2 diabetes and affective disorders have complex (i.e., mediating or moderating) relationships with one another. In addition, affective disorders themselves can present as chronic or episodic conditions. Their relationship may alternately be conceptualized as an accumulation of risk over an individual's lifetime, through either trajectories or chains of risk precipitated by psychiatric symptoms (39). A clearer understanding of anxious symptomatology and its correlates would help to explain the differences observed here, as well as to clarify the inconsistent findings around anxiety and mortality that persist in the literature.

6.4.2 Strengths and Limitations

Research based on this survey may also not easily generalize to other populations, as Nord-Trøndelag is a rural county, which demonstrates little ethnic heterogeneity and a lower prevalence of diabetes when compared to most developed countries. As with many cohort studies, the current study design is vulnerable to the presence of unmeasured confounders, such as baseline metabolic syndrome or prediabetes status. Similarly, although participation was relatively high, non-participation in the study may be linked to mortality. The latter two factors are expected to bias our results towards the null, however, rather than overinflate our estimates.

Another possible limitation of the HUNT data is that symptoms of depression and anxiety were measured by self-report rather than diagnostic interview. “High” symptom levels defined here may represent sub-threshold levels for their respective diagnoses; however both minor depression and sub-threshold symptoms have demonstrated associations with excess mortality comparable to major depression (40). This study also does not consider the duration of diabetes or affective symptoms at baseline, which may have the potential to exert moderating effects on the observed relationships.

Despite these limitations, this study had substantial strengths. These included data on a comprehensive range of confounders and a reliable source for mortality data, on a relatively large study population. A generous follow-up time allowed us to illustrate that high baseline levels of affective symptoms are associated with increased mortality spanning 18 years, with pronounced effects in individuals with Type 2 diabetes. The inclusion of anxious symptoms allowed us to estimate their associations with mortality risk independently of symptoms of depression. These findings point to the potential usefulness of research examining sex-specific differences in the clinical features of anxiety and depression in individuals with Type 2 diabetes.

Funding

This work was supported in part by funding from the Canada Research Chairs program for IC, and by an Ontario Mental Health Foundation doctoral award held by KN. JAJ holds a Senior Health Scholar award from Alberta Innovates Health Solutions.

Table 6.1: Baseline sociodemographic and health characteristics of HUNT 2 participants, by Type 2 diabetes status, 1995-1997 (N=64,177)

	Individuals without Diabetes (n=63,044)	Individuals with Type 2 Diabetes (n=1,133)	P-value
Age (mean, SD)	49.47 (17.0)	68.31 (11.1)	**<0.001**
Sex (Female)	53.28%	50.45%	0.100
Education (Low)	70.00%	90.44%	**<0.001**
Mental Health Symptoms (High)	5.18%	13.35%	**<0.001**
Depression Only	9.29%	22.86%	**<0.001**
Anxiety Only	7.18%	10.10%	**<0.001**
Depression-Anxiety			
Waist circumference (High)*	45.34%	80.16%	**<0.001**
Physical activity (Inactive)†	52.43%	62.07%	**<0.001**
Smoking			
Non-smoker	43.47%	44.65%	**<0.001**
Former Daily Smoker	27.18%	39.45%	
Current Daily Smoker	29.35%	15.89%	
Family History of diabetes (Yes)	14.56%	44.80%	**<0.001**
Chronic Conditions (Yes)	21.10%	46.59%	**<0.001**
Baseline antidepressant use (Yes)	2.79%	4.00%	**0.01**
Baseline insulin use (Yes)	-	18.7%	**-**
Died During Follow-Up	19.87%	65.26%	**<0.001**

Abbreviations: SD, standard deviation

* Waist circumference: ≥94 cm for men, ≥80 cm for women

† ≤150 minutes of moderate or ≤60 of vigorous physical activity per week

Table 6.2: Hazard ratios (HRs) for mortality risk over 18 years associated with baseline type 2 diabetes status and comorbid symptoms of anxiety and depression, by sex (HUNT 2 Study, 1995-2013)

	ALL (N=64,177)				WOMEN (n=34,116)		MEN (n=30,061)	
	Unadjusted HR*	95% CI	Adjusted HR†	95% CI	Adjusted HR†	95% CI	Adjusted HR†	95% CI
Type 2 Diabetes and Depression								
No diabetes, low DEP	(ref)		(ref)		(ref)		(ref)	
No diabetes, high DEP	1.37	1.26, 1.50	1.27	1.14, 1.41	1.26	1.08, 1.46	1.26	1.08, 1.47
Diabetes, low DEP	1.64	1.41, 1.71	1.50	1.32, 1.70	1.86	1.53, 2.26	1.31	1.10, 1.55
Diabetes, high DEP	2.76	2.00, 3.84	2.10	1.41, 3.13	1.95	1.22, 2.72	3.47	1.96, 6.14
Type 2 Diabetes and Anxiety								
No diabetes, low ANX	(ref)		(ref)		(ref)		(ref)	
No diabetes, high ANX	1.30	1.21, 1.38	1.20	1.11, 1.30	1.21	1.08, 1.34	1.20	1.06, 1.34
Diabetes, low ANX	1.52	1.37, 1.69	1.44	1.26, 1.65	1.82	1.48, 2.25	1.26	1.06, 1.51
Diabetes, high ANX	1.99	1.57, 2.53	1.66	1.25, 2.19	1.38	0.95, 2.01	2.14	1.41, 3.27
Type 2 Diabetes and Concurrent Depression-Anxiety								
No T2D, low DEP-ANX	(ref)		(ref)		(ref)		(ref)	
No T2D, high DEP-ANX	1.37	1.23, 1.56	1.22	1.07, 1.40	1.15	1.05, 1.39	1.27	1.04, 1.53
T2D, low DEP-ANX	1.56	1.45, 1.69	1.44	1.29, 1.60	1.65	1.40, 1.95	1.30	1.12, 1.51
T2D, high DEP-ANX	2.56	1.73, 3.79	2.01	1.18, 3.00	1.14	0.57, 2.29	3.42	1.84, 6.38

*Adjusted for age, sex

†Adjusted for age, sex, education, waist circumference, physical activity, smoking, antidepressant use, insulin use, family history of diabetes, chronic conditions

Abbreviations: DEP, depressive symptoms; ANX, anxious symptoms; DEP-ANX, concurrent depressive and anxious symptoms.

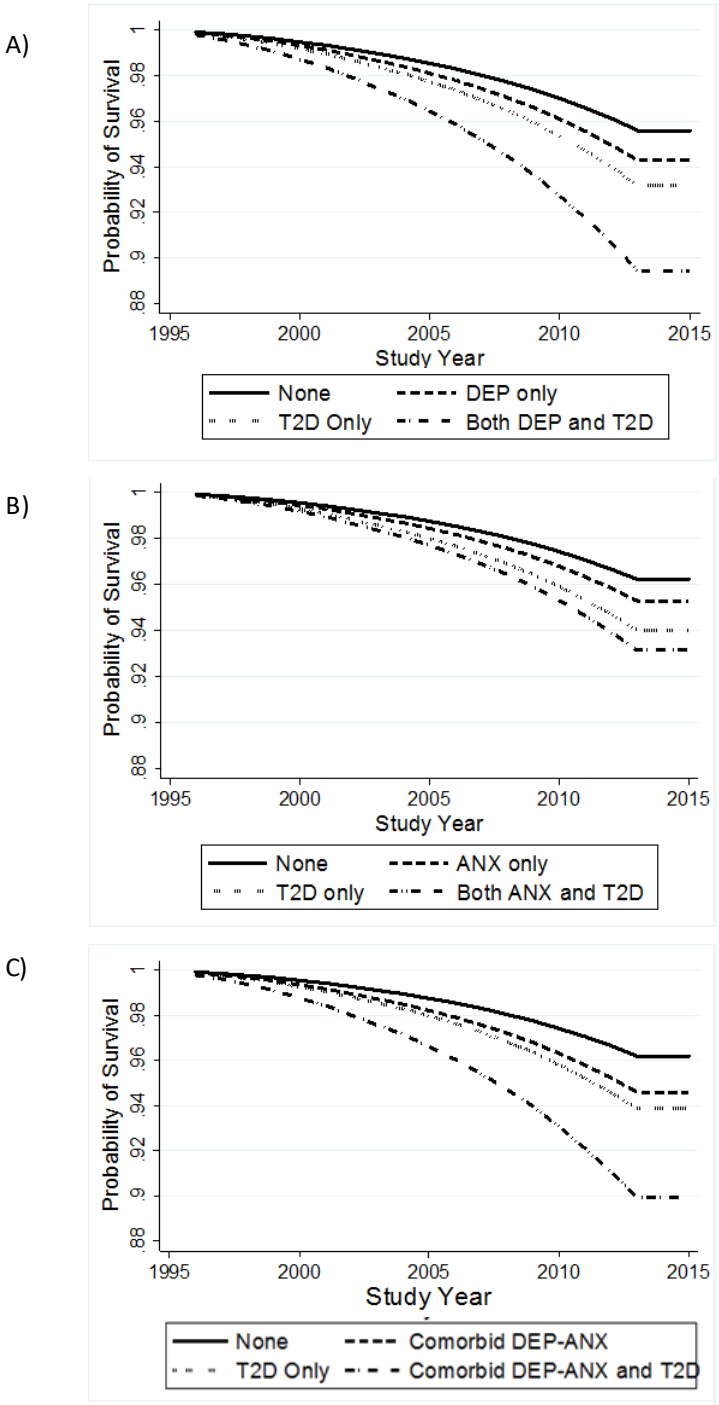


Figure 6.1: Kaplan-Meier survival curve illustrating adjusted mortality risk over 18 years associated with type 2 diabetes status and baseline symptoms of anxiety and depression (HUNT 2 Study, 1995-2013). A) Deaths in participants with and without depression (DEP) and Type 2 diabetes (T2D). B) Deaths in participants with and without anxiety (ANX) and T2D. C) Deaths in participants with and without concurrent depression-anxiety (DEP-ANX) and T2D.

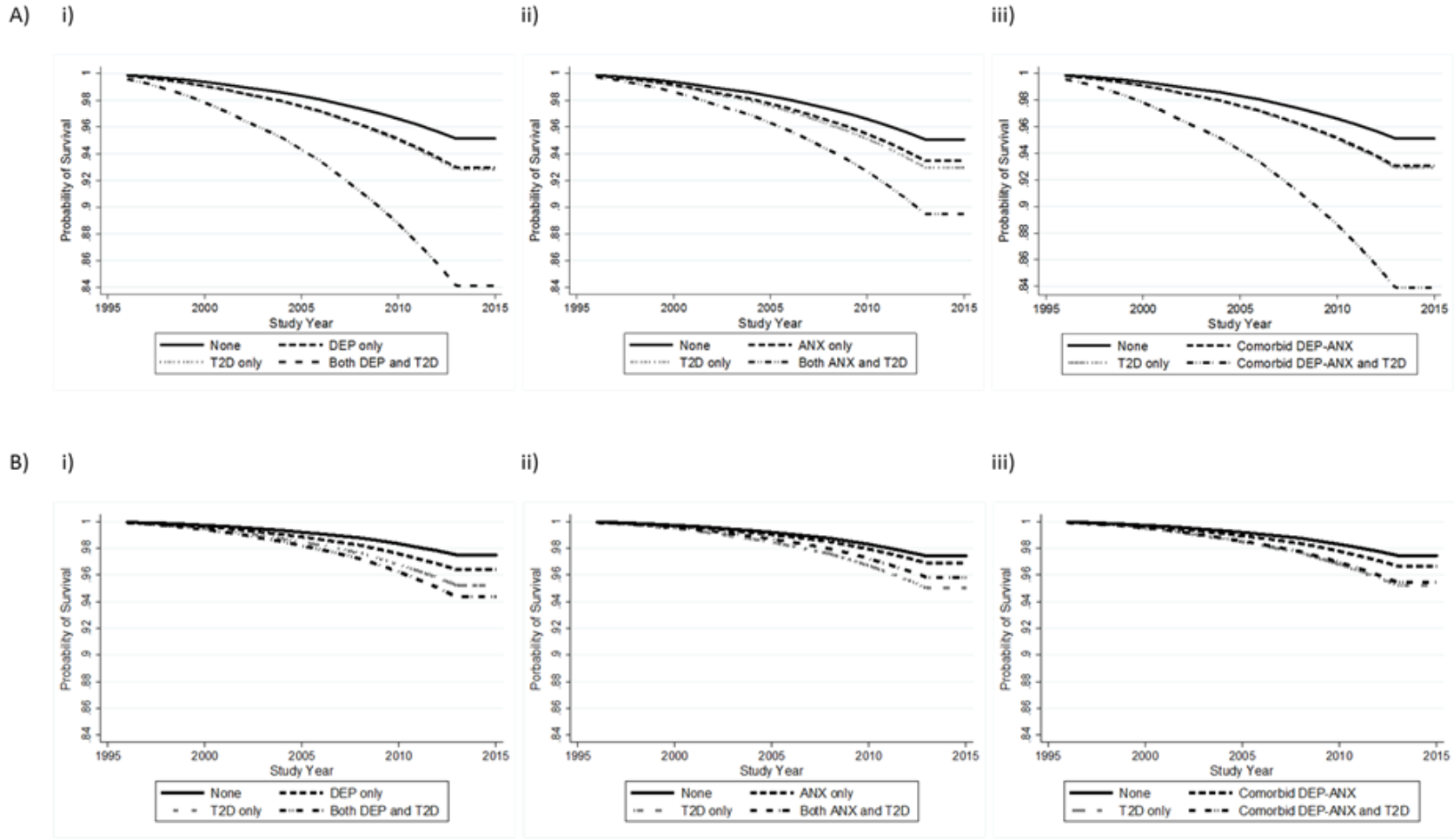
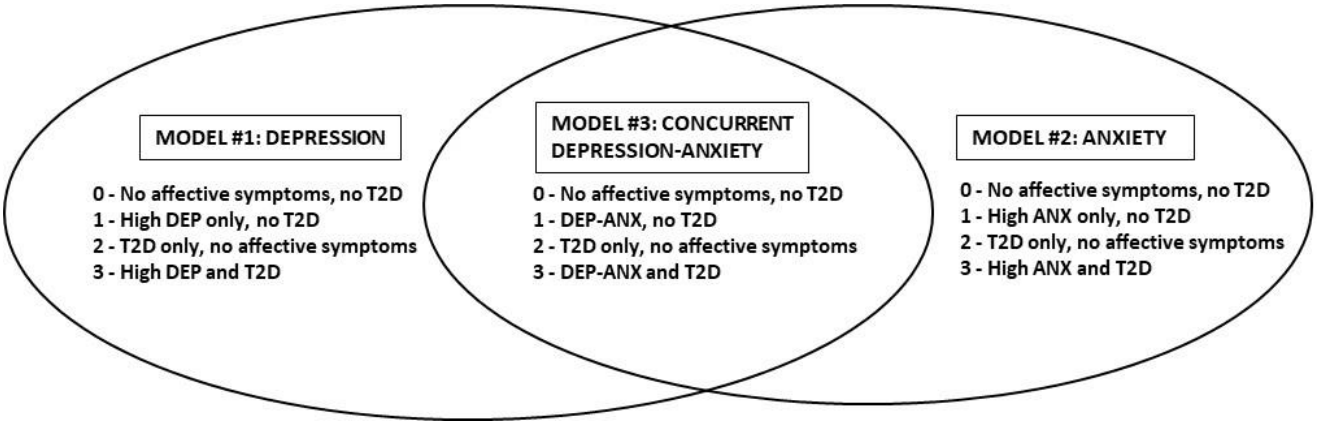


Figure 6.2: Kaplan-Meier curves demonstrating survival over 18 years associated with type 2 diabetes and symptoms of anxiety and depression, by sex (HUNT Study, 1995-2013). A) Deaths in men with and without type 2 diabetes and symptoms of i) depression, ii) anxiety and iii) concurrent depression-anxiety (n=30, 061). B) Corresponding deaths in women (n=34, 116). Abbreviations: DEP, depressive symptoms; ANX, anxious symptoms; DEP-ANX, concurrent depressive and anxious symptoms.

Table 6.3: Adjusted hazard ratios (HRs) for mortality risk over 18 years associated with baseline symptoms of anxiety and depression in individuals with Type 2 diabetes only, by sex (HUNT 2 Study, 1995-2013)

	Women (n=575)		Men (n=558)		All (N=1,133)	
Affective Symptom Type	**HR***	**95% CI**	**HR***	**95% CI**	**HR***	**95% CI**
Depression	1.36	0.86, 2.17	**2.47**	**1.47, 4.17**	**1.67**	**1.18, 2.36**
Anxiety	1.10	0.77, 1.57	**1.63**	**1.08, 2.47**	1.30	0.99, 1.69
Concurrent Depression-Anxiety	1.28	0.85, 1.93	**2.23**	**1.38, 3.59**	**1.58**	**1.16, 2.15**

*Adjusted for age, sex, education, waist circumference, physical activity, smoking, antidepressant use, insulin use, family history of diabetes, chronic conditions



Supplementary Figure 6.1: Predictor variable categories corresponding to the three main study models. Abbreviations: T2D, Type 2 diabetes; DEP-ANX, concurrent depressive and anxious symptoms.

REFERENCES

1. Organization WH. Global status report on noncommunicable diseases 2014. Geneva. 2012.
2. Marcus M, Yasamy M, Ommeren M van. Depression: A global public health concern. Retrieved Febr. 2012;
3. Semenkovich K, Brown ME, Svrakic DM, Lustman PJ. Depression in type 2 diabetes mellitus: prevalence, impact, and treatment. Drugs. 2015 Apr;75(6):577–87.
4. Hirschfeld R. The comorbidity of major depression and anxiety disorders: recognition and management in primary care. Primary Care Companion to the Journal of Clinical Psychiatry. 2001; 244-254
5. Hofmeijer-Sevink MK, Batelaan NM, van Megen HJGM, Penninx BW, Cath DC, van den Hout MA, et al. Clinical relevance of comorbidity in anxiety disorders: a report from the Netherlands Study of Depression and Anxiety (NESDA). Journal of Affective Disorders. 2012 Mar;137(1-3):106–12.
6. Cuijpers P, Schoevers RA. Increased mortality in depressive disorders: A review. Current Psychiatry Reports. 2004 Dec;6(6):430–7.
7. Saeed Mirza S, Ikram MA, Hofman A, Tiemeier H. Anxiety does not predict mortality. A population-based study. World Psychiatry. 2015 Feb;14(1):103–4.
8. Lee WE, Wadsworth MEJ, Hotopf M. The protective role of trait anxiety: a longitudinal cohort study. Psychological Medicine. 2006 Jan 5;36(03):345.
9. Eaton WW, Roth KB, Bruce M, Cottler L, Wu L, Nestadt G, et al. The relationship of mental and behavioral disorders to all-cause mortality in a 27-year follow-up of 4 epidemiologic catchment area samples. American Journal Epidemiology. 2013 Nov 1;178(9):1366–77.
10. Walker ER, McGee RE, Druss BG. Mortality in Mental Disorders and Global Disease Burden Implications: A Systematic Review and Meta-analysis. JAMA Psychiatry. 2015 Feb 11;72(4):334–41.
11. Zheng D, Macera CA, Croft JB, Giles WH, Davis D, Scott WK. Major depression and all-cause mortality among white adults in the United States. Annals of Epidemiology. 1997 Apr;7(3):213–8.
12. Murphy JM, Burke JD, Monson RR, Horton NJ, Laird NM, Lesage A, et al. Mortality associated with depression: a forty-year perspective from the Stirling County Study. Social Psychiatry and Psychiatric Epidemiology. 2008 Aug;43(8):594–601.
13. SCHOEVERS RA. Association of depression and gender with mortality in old age: Results from the Amsterdam Study of the Elderly (AMSTEL). British Journal of Psychiatry. 2000 Oct 1;177(4):336–42.
14. Penninx BWJH, Geerlings SW, Deeg DJH, van Eijk JTM, van Tilburg W, Beekman ATF. Minor and Major Depression and the Risk of Death in Older Persons. Archives of General Psychiatry. 1999 Oct 1;56(10):889.
15. van Hout HPJ, Beekman ATF, de Beurs E, Comijs H, van Marwijk H, de Haan M, et al. Anxiety

and the risk of death in older men and women. British Journal of Psychiatry. 2004 Nov 1;185(5):399–404.

16. DiMatteo MR, Lepper HS, Croghan TW. Depression Is a Risk Factor for Noncompliance With Medical Treatment. Archives of Internal Medicine. 2000 Jul 24;160(14):2101.

17. Branney P, White A. Big boys don't cry: depression and men. Advances in Psychiatric Treatment. 2008 Jul 1;14(4):256–62.

18. Cherrington A, Wallston KA, Rothman RL. Exploring the relationship between diabetes self-efficacy, depressive symptoms, and glycemic control among men and women with type 2 diabetes. Journal of Behavioural Medicine. 2010 Feb;33(1):81–9.

19. Vogelzangs N, Beekman ATF, de Jonge P, Penninx BWJH. Anxiety disorders and inflammation in a large adult cohort. Translational Psychiatry. 2013 Jan 23;3:e249.

20. Krokstad S, Langhammer A, Hveem K, Holmen TL, Midthjell K, Stene TR, et al. Cohort Profile: the HUNT Study, Norway. International Journal of Epidemiology. 2013 Aug 1;42(4):968–77.

21. Pedersen AG, Ellingsen CL. Data quality in the Causes of Death Registry. Tidsskr den Nor lægeforening Tidsskr Prakt Med ny række. 2015 May 5;135(8):768–70.

22. Søgaard A, Bjelland I, Tell G, Røysamb E. A comparison of the CONOR Mental Health Index to the HSCL-10 and HADS. Norsk Epidemioli. 2003;

23. Staiano AE, Reeder BA, Elliott S, Joffres MR, Pahwa P, Kirkland SA, et al. Body mass index versus waist circumference as predictors of mortality in Canadian adults. International Journal of Obesity. 2012 Nov;36(11):1450–4.

24. Mykletun A, Overland S, Aarø LE, Liabø H-M, Stewart R. Smoking in relation to anxiety and depression: evidence from a large population survey: the HUNT study. European Psychiatry. 2008 Mar;23(2):77–84.

25. Yeh H-C, Duncan BB, Schmidt MI, Wang N-Y, Brancati FL. Smoking, smoking cessation, and risk for type 2 diabetes mellitus: a cohort study. Annals of Internal Medicine. 2010 Jan 5;152(1):10–7.

26. Kenfield SA, Stampfer MJ, Rosner BA, Colditz GA. Smoking and smoking cessation in relation to mortality in women. JAMA. 2008 May 7;299(17):2037–47.

27. Chang M, Hahn RA, Teutsch SM, Hutwagner LC. Multiple risk factors and population attributable risk for ischemic heart disease mortality in the United States, 1971–1992. Journal of Clinical Epidemiology. 2001 Jun;54(6):634–44.

28. Cleves M. An Introduction to Survival Analysis Using Stata, Second Edition. Stata Press; 2008. 372.

29. Harrell FE. General Aspects of Fitting Regression Models. In 2001. p. 11–40.

30. Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. Lancet. 2007 Sep 8;370(9590):

31. Egede LE. Major depression in individuals with chronic medical disorders: prevalence, correlates and association with health resource utilization, lost productivity and functional disability. General

Hospital Psychiatry. 2007 Jan;29(5):409–16.

32. Moulton CD, Pickup JC, Ismail K. The link between depression and diabetes: the search for shared mechanisms. The Lancet Diabetes & Endocrinology. 2015 May;3(6):461–71.

33. Safren SA, Gonzalez JS, Wexler DJ, Psaros C, Delahanty LM, Blashill AJ, et al. A randomized controlled trial of cognitive behavioral therapy for adherence and depression (CBT-AD) in patients with uncontrolled type 2 diabetes. Diabetes Care. 2014 Jan 1;37(3):625–33.

34. Holwerda TJ, Schoevers RA, Dekker J, Deeg DJH, Jonker C, Beekman ATF. The relationship between generalized anxiety disorder, depression and mortality in old age. International Journal of Geriatric Psychiatry. 2007 Mar;22(3):241–9.

35. Hu WHC, Wong W-M, Lam CLK, Lam KF, Hui WM, Lai KC, et al. Anxiety but not depression determines health care-seeking behaviour in Chinese patients with dyspepsia and irritable bowel syndrome: a population-based study. Alimentary Pharmacology and Therapeutics. 2002 Dec;16(12):2081–8.

36. Park M, Katon WJ, Wolf FM. Depression and risk of mortality in individuals with diabetes: a meta-analysis and systematic review. General Hospital Psychiatry.2013 Jan 5;35(3):217–25.

37. Hofmann M, Köhler B, Leichsenring F, Kruse J. Depression as a risk factor for mortality in individuals with diabetes: a meta-analysis of prospective studies. PLoS One. Public Library of Science; 2013 Jan 21;8(11):e79809.

38. van Dooren FEP, Nefs G, Schram MT, Verhey FRJ, Denollet J, Pouwer F. Depression and risk of mortality in people with diabetes mellitus: a systematic review and meta-analysis. PLoS One. 2013 Jan;8(3):e57058.

39. Pillas D, Naicker K. Public health, policy, and practice: implications of life course approaches to mental illness. A Life Course Approach to Mental Illness 2013;

40. Cuijpers P, Vogelzangs N, Twisk J, Kleiboer A, Li J, Penninx BW. Differential mortality rates in major and subthreshold depression: meta-analysis of studies that measured both. British Journal of Psychiatry. 2013 Jan 1;202(1):22–7.

Appendix 6A: Sensitivity analysis comparing imputed and unimputed adjusted hazard ratios (HRs) for mortality risk over 18 years associated with baseline type 2 diabetes status and symptoms of anxiety and depression, by sex

	WOMEN (n=34,116)				MEN (n=30,061)			
	Imputed HR* [95% CI]		Unimputed HR† [95% CI]		Imputed HR* [95% CI]		Unimputed HR† [95% CI]	
Type 2 Diabetes and Depression								
No diabetes, low DEP	(ref)		(ref)		(ref)		(ref)	
No diabetes, high DEP	1.26	1.08, 1.46	1.33	1.11, 1.59	1.26	1.08, 1.47	1.39	1.17, 1.66
Diabetes, low DEP	1.86	1.53, 2.26	1.96	1.57, 2.44	1.31	1.10, 1.55	1.43	1.18, 1.72
Diabetes, high DEP	1.95	1.22, 2.72	2.24	1.20, 2.20	3.47	1.96, 6.14	3.45	1.85, 6.43
Type 2 Diabetes and Anxiety								
No diabetes, low ANX	(ref)		(ref)		(ref)		(ref)	
No diabetes, high ANX	1.21	1.08, 1.34	1.17	1.03, 1.34	1.20	1.06, 1.34	1.28	1.13, 1.47
Diabetes, low ANX	1.82	1.48, 2.25	1.99	1.58, 2.52	1.26	1.06, 1.51	1.43	1.18, 1.73
Diabetes, high ANX	1.38	0.95, 2.01	1.65	0.97, 2.07	2.14	1.41, 3.27	2.48	1.55, 3.63
Type 2 Diabetes and Concurrent Depression-Anxiety								
No T2D, low DEP-ANX	(ref)							
No T2D, high DEP-ANX	1.15	1.05, 1.39	1.23	0.99, 1.52	1.27	1.04, 1.53	1.35	1.17, 1.78
T2D, low DEP-ANX	1.65	1.40, 1.95	1.96	1.60, 2.04	1.30	1.12, 1.51	1.43	1.19, 1.72
T2D, high DEP-ANX	1.14	0.57, 2.29	1.55	0.73, 3.22	3.42	1.84, 6.38	3.53	1.76, 7.08

*Adjusted for age, sex, education, waist circumference, physical activity, smoking, antidepressant use, insulin use, family history of diabetes, chronic conditions

†Refers to results from a complete-case analyses

Appendix 6B. STROBE Statement

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	153-154
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	154
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	155
Objectives	3	State specific objectives, including any prespecified hypotheses	156
Methods			
Study design	4	Present key elements of study design early in the paper	157
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	157
Participants	6	*(a) Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	157
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	157-160
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	157-160
Bias	9	Describe any efforts to address potential sources of bias	160
Study size	10	Explain how the study size was arrived at	157
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	157-160
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	160
		(*b*) Describe any methods used to examine subgroups and interactions	160
		(*c*) Explain how missing data were addressed	160
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	160
		(*e*) Describe any sensitivity analyses	176

Appendix 6B. STROBE Statement (continued)

Results			**Page**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	161, 167
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	161, 167
		(b) Indicate number of participants with missing data for each variable of interest	85
		(c) Cohort study—Summarise follow-up time	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	161,167
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	168
		(*b*) Report category boundaries when continuous variables were categorized	168
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	162, 171
Discussion			
Key results	18	Summarise key results with reference to study objectives	163-166
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	165-166
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	165-166
Generalisability	21	Discuss the generalisability (external validity) of the study results	165
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	166

Appendix 6C. Screenshot of manuscript acceptance letter from *Diabetes Care*

Decision Letter (DC16-2018.R1)

From:

To:

CC:

Subject: Letter of Acceptance - DC16-2018.R1

Body: RE: Original Article - Type 2 Diabetes and Comorbid Symptoms of Depression and Anxiety: Longitudinal Associations with Mortality Risk

Submitted 19-Sep-2016 and accepted

11-Dec-2016

Dr. Ian Colman,
University of Ottawa
School of Epidemiology, Public Health and Preventive Medicine
Ottawa, Ontario K1H 8M5 Canada

Dear Dr. Colman:

We are pleased to inform you that your manuscript has been accepted for publication in Diabetes Care.

Congratulations!

Your paper is being processed and sent to Production. Notification of proof page availability and information regarding reprint orders will be sent via e-mail to the corresponding author in approximately 30-45 days. (Please note that only the corresponding author designated on the title page of the manuscript will receive this notification.)

Diabetes Care publishes original research articles online ahead of the final print and online issue approximately 30-45 days from receipt of your proof corrections.

If your institution is considering issuing a press release about your article and you would like to coordinate the date for online publication to coincide with the press release, please contact Content Production Manager Kelly Newton at knewton@diabetes.org.

Accepted articles funded by the National Institutes of Health (NIH) or authored by an employee of NIH will be deposited in PubMed Central, a repository of peer-reviewed research maintained by NIH. Articles will be accessible on PubMed Central 12 months after the date of final print/online publication in Diabetes Care. Articles will be freely accessible on Diabetes Care Online 6 months after publication. Authors are permitted to immediately submit the final accepted version of their manuscript to their institution's or funding body's internal repository, provided proper attribution to Diabetes Care is given.

We thank you for submitting your interesting work to Diabetes Care and look forward to receiving additional manuscripts from you in the future. In addition, we hope that you will help us maintain the high standards of Diabetes Care by agreeing to serve as a reviewer if we should call upon you in the future. Thank you!

Sincerely,

William T. Cefalu, M.D., Editor-in-Chief, Diabetes Care
Executive Director
Pennington Biomedical Research Center
Baton Rouge, LA 70808-4124

Please respond to: DiabetesCare@diabetes.org

Appendix 6D. Ethical approval from HUNT Study committee for manuscript

NTNU

Det medisinske fakultet
Institutt for samfunnsmedisin

Vår dato 07.04.2016 | Vår referanse 2014/22653/TRS
Deres dato | Deres referanse

Børge Sivertsen
Avdeling for samfunn og psykisk helse
Nasjonalt folkehelseinstitutt
Boks 4404 Nydalen
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HUNT publikasjonsutvalg

Manus: *Type 2 diabetes and comorbidi symptoms of depression and anxiety: Longitudinal associations with mortality risk*
Forfattere: *Naicker K, Øverland S, Johnson J, Skogen J, Manuel D, Sivertsen B, Colman I*
Datert: *060416*

Publikasjonsutvalget har vurdert manuset ut fra den inngåtte avtalen om analyserettigheter til HUNT-data og retningslinjene for forvaltning og bruk av data og har følgende kommentar:
Ifølge Retningslinjene for publisering av forskningsresultater som bruker HUNT-data kreves det at HUNT synliggjøres i tittel på publikasjonene. Se vedlagte kopi av retningslinjene for forslag til tekst.

Manuset godkjennes for publisering når ovennevnte punkt er endret.

Publikasjonsutvalget ønsker kopi av artikkelen så snart den foreligger.

Med hilsen

Turid Rygg Stene
rådgiver

Inger D. Holbø
førstekonsulent

Vedlegg: Retningslinjer for publisering av forskningsresultater som bruker HUNT-data

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CHAPTER 7:

GENERAL DISCUSSION

This chapter presents a summary of the findings of the four preceding papers and answers to the specific study research questions introduced in Chapter 1 (listed in Table 7.1). A general discussion of the findings and their implications with respect to the wider epidemiological literature is provided. This is followed by a discussion of the strengths and limitations of the thesis as a whole, and lastly, by suggested directions for future research and final conclusions.

7.1 Summary of Research Findings

7.1.1 Depression and anxiety in diabetes onset (Chapters 2 and 4)

The meta-analysis of longitudinal studies presented in Chapter 2 demonstrated the overall pooled relative risk of incident diabetes associated with depression in the literature to be between 1.53 and 1.81 (depending on the level of adjustment of the models), which is in the range of previous meta-analyses conducted on this association [1–4]. Novel to our study was the finding that these estimates appear to be higher in men and non-significant in women when stratified by sex. The pooled relative risk of Type 2 diabetes associated with anxiety was between 1.13 and 1.30 (depending on the level of adjustment), which also constituted a unique finding. This estimate was again found to be much higher in men (2.31) and non-significant in women. The comprehensive literature search undertaken in this study failed to uncover any longitudinal research examining the effects of concurrent depression and anxiety on diabetes onset, and exposed a relative paucity

of studies on anxiety compared to the number of studies on depression, as well as a lack of studies that adjusted for the concurrent presence of anxiety in their design. Larger effect sizes were noted in studies that controlled for antidepressant use, had shorter follow-up times (>10 years), and used clinical diagnostic interviews rather than self-report to measure depression and anxiety.

The article presented in Chapter 4 sought to examine diabetes incidence associated with the above psychological risk factors in a large population-based sample of Norwegian adults. As risk factors often cluster in reality, the purpose of this study was to determine the proportion of incident diabetes cases attributable to both individual factors and combinations of multiple factors, including the metabolic syndrome, behavioural factors, and symptoms of depression and anxiety. Overall, 1,324 incident diabetes cases occurred during this 11-year period. The studied risk factors accounted for 78.2% of all incident diabetes cases in men, and 47.0% of incident cases in women. A small proportion of individuals did not display any other metabolic or behavioural risk factors; in these individuals, symptoms of depression accounted for 2.0% of incident cases in men, and concurrent depression-anxiety accounted for 0.9%. Anxious symptoms were not associated with any new cases in the absence of other risk factors. The impact of either of these factors alone on diabetes incidence in women was negligible. The largest fraction of diabetes cases due to a single factor was attributable to the metabolic syndrome in women (9.8%) and lifestyle factors in men (8.9%). In combination with one another, the metabolic syndrome and behavioural factors accounted for over 20% of new cases in both men and women.

However, the symptoms of depression and/or anxiety added another 17.1% of new cases to the latter combination in men, and another 10.2% of cases in women. Behavioural factors (i.e.,

smoking and physical inactivity) in combination with depression conferred another 10.9% of cases in men (with another 2.1% and 2.0% attributable to anxiety and to concurrent depression-anxiety, respectively). While the relative risks of diabetes onset associated with baseline depression (alone or in combination) were higher than those associated with anxiety, a larger percentage of new cases overall was attributable to anxiety, primarily due to a higher in prevalence the study population. The presence of all four factors (i.e., metabolic, lifestyle, depression and anxiety) was associated with the highest (i.e., over seven-fold) increase in diabetes risk, and although the prevalence of this combination was relatively low in the population, it contributed 6.2% of diabetes cases overall.

The above findings all represent original contributions to the literature, as no studies have yet attempted to quantify the excess fraction of incident diabetes associated with the co-occurrence of psychological and traditional risk factors. Moreover, this study was unique in its design and presentation of results, which allowed a more nuanced illustration of how psychological, metabolic and behavioural factors may work together to increase diabetes risk than has been done to date. These results imply that, while psychological factors on their own may not pose substantial risk of Type 2 diabetes onset, they represent important modifiable factors that work in concert with other traditional factors to increase the burden of the disease.

7.1.2 Depression and anxiety in diabetes management (Chapter 5)

The next original study (Chapter 5) presented a cross-sectional examination of a range of clinical and self-management outcomes in 2,035 adults with Type 2 diabetes. Of the 14 outcomes studied (e.g., central obesity, HDL cholesterol, glucose monitoring at home, etc.), the majority were not significantly associated with symptoms of depression or anxiety. However, several associations

were of interest, especially in the results of the sex-stratified analysis. In women, anxiety symptoms (both alone and in combination with depression) were associated with elevated C-reactive protein levels, and with a behavioural tendency to avoid eating saturated fats. In men, depressive symptoms (both alone and in combination with anxiety) were associated with a three- to five-fold increase in odds of experiencing poor glycemic control. These differences were robust to formal tests of interaction by sex. Symptoms of depression, anxiety, and concurrent depression-anxiety were also universally associated with lower odds of exercising weekly and with reporting a negative subjective diabetes experience in men and women. Concurrent depression-anxiety was not substantially associated with the odds of negative outcomes above either symptom group alone. Overall, these results suggest the potential importance of differentiating between psychological symptoms of depression and anxiety in the management of Type 2 diabetes cases.

7.1.3 Depression and anxiety and mortality in Type 2 diabetes (Chapter 6)

The final study (Chapter 6) followed over 64,000 Norwegian adults over 18 years to determine the effects of these psychological exposures on longevity in individuals with and without Type 2 diabetes. This study used a linkage with the Norwegian National Causes of Death Registry to assess the excess risk of mortality associated with the baseline presence of depression, anxiety and diabetes, alone and in combination with one another. We observed clear trends in mortality risk with respect to the type of affective symptom experienced, with depression conferring the highest excess risk and anxiety attenuating this relationship downwards. This finding was novel, since although previous research has examined mortality risk associated with baseline depression and diabetes status [5–7], no studies to date have explored this relationship with respect to symptoms

of anxiety or concurrent depression-anxiety. In further analysis, these risks were revealed to be elevated in men and nonsignificant in women, which constituted another novel finding. Overall, this study demonstrates a role for anxiety in attenuating the long-term effects of depression on mortality in men with Type 2 diabetes.

Table 7.1: Key findings of the four thesis studies

Study	Key Findings
Chapter 2 (Study 1)	• According to high quality studies that control for similar covariates, baseline depression was associated with an 81% increased risk of Type 2 diabetes onset; baseline anxiety with a 30% increased risk. • The increased risk with anxiety was independent of the presence of depression, but it is unclear whether the reverse is true. • These effects are larger in men and non-significant in women. • No studies have examined the effect of concurrent depression-anxiety on diabetes onset.
Chapter 4 (Study 2)	• In the absence of metabolic or behavioural risk factors, a very small percentage of diabetes cases (< 3%) are attributable to depression, anxiety, and concurrent depression-anxiety in men. • No cases are attributable to these factors alone in women. • The largest proportion of incident cases was attributed to the presence of metabolic syndrome plus behavioural factors (22.9%). • Depression, anxiety and depression-anxiety added another 13.6% of cases to this combination (2.5%, 4.9%, and 6.2%, respectively) • A larger fraction of new diabetes cases are attributable to the presence of depression and anxiety in men than in women.
Chapter 5 (Study 3)	• Symptoms of depression and anxiety are not independently associated with many clinical and behavioural diabetes outcomes. • However, these factors are universally associated with physical inactivity and a poorer subjective experience of diabetes. • Depression is strongly associated with indicators of glycemic control in men. Concurrent anxiety increases these odds even further. • Anxious symptoms are associated with C-reactive protein levels and avoiding saturating fat consumption, but only in women.
Chapter 6 (Study 4)	• Mortality risk in diabetic individuals is lowest in those with baseline anxiety, higher for depression-anxiety, and highest for depression. • Depression increases the risk of mortality in men with diabetes by almost 2.5 times. Anxiety slightly attenuates this association. • Neither symptoms of depression nor anxiety confer significantly increased mortality risks in women with diabetes.

7.2 Discussion and Implications

7.2.1 Sex-specific reporting of findings in studies of depression, anxiety and diabetes

The extensive literature reviews conducted in Chapters 1 and 2 uncovered a lack of sex-specific research or analysis in this area, with less than 10% of studies included in previous meta-analyses reporting sex-specific findings [8]. In contrast, all four of the original studies presented in this thesis demonstrated differences between men and women with respect to key diabetes outcomes, each using a different study sample. Formal tests of interaction by sex conducted in the latter studies were all significant. Overall, associations between depression and diabetes outcomes appeared to be much stronger in men and potentially nonsignificant in women.

Although diabetes is diagnosed more frequently and often at younger ages and at lower body mass indices in men [9], as noted by Demmer and colleagues, surprisingly few studies to date have reported sex-specific results in associations between depression, anxiety and Type 2 diabetes [8]. This observation may help to clarify the heterogeneity of results observed in the wider literature on this topic, and may partially explain the findings of previous studies which have failed to demonstrate a relationship between depression or anxiety and diabetes. For example, in the case of one study by Saydah and colleagues (2003), of the baseline 'high' depression exposure group, 76% of the participants were women, yet sex-stratified results were not calculated [10]. The authors reported a lack of association between depression and incident diabetes [10]. A similar phenomenon was observed in another study, where roughly equal proportions (~50%) of men and women made up the non-depressed group, but those classified at baseline as being depressed (i.e., the exposed group) were over 70% women. The authors do not stratify their results, where they

found no association in this study between depression and diabetes over a 3-year follow-up [11]. Again, a third study reported roughly 50% men in the non-depressed group at baseline, but close to 70% of the group above the threshold for depression at baseline were women; the authors did not stratify by sex and did not find an association between depression and diabetes onset. A fourth study with similar nonsignificant findings not only did not stratify by sex, but did not report the proportion of men and women making up the study sample altogether [12].

These observations point to the possibility that women may have a tendency to dominate the 'exposed' group in studies of depression or anxiety, due to the higher prevalences of mood disorders reported by women [13, 14]. In addition to the higher prevalences of depression observed in women, depression symptoms are also often more common among women than men [15], and men report fewer symptoms than women even after stratification by clinically significant levels of impairment [13]. Although women consistently have higher documented rates of anxiety and mood disorders, little is still known about how gender affects age of onset, prognoses, comorbidity, and burden of mental illness [16]. The gender differences in rates between men and women first emerge during puberty [14], and are shown to be due to higher risk of first onset, rather than differences in chronicity or recurrence.

It has been suggested that the key to understanding the higher rates of depression among women lies in an investigation of the joint effects of biological vulnerabilities and environmental experiences [14]. Given the major endocrinological changes that occur throughout female development, these associations may also fluctuate over the life course. A study of the effect of depressive symptoms during adolescence found that early onset depression is associated with

incident diabetes in in females during a 13-year follow-up, but not males (OR=1.96 versus OR=0.86) [17]. Interestingly, while depression is linked to low testosterone levels in men [18], increased testosterone during puberty in girls is linked to depression [19]. Further research demonstrates that endogenous sex hormones have a large impact on metabolism and body composition, and may moderate glycemic status, with high testosterone levels increasing Type 2 diabetes risk in women but decreasing risk in men [9, 20]. It may be plausible then that women experiencing excesses of androgen hormones during puberty may represent a subset of women vulnerable to both early onset of depressive disorders, and subsequent Type 2 diabetes. While this example likely only applies to a small proportion of individuals, it illustrates that gender inequalities in diabetes outcomes do exist, and involve a complex interplay of endocrine and behavioural factors [9].

Of higher concern is the fact that the findings of this thesis support the notion that, despite the higher prevalences of depression reported in women, depressed men have higher risks of developing associated diabetes. There is also evidence of this in the literature, with one study reporting that, although the prevalence of depression in their sample was almost double in females with diabetes compared with males (23.8% versus 12.8%), the odds of depression in individuals with diabetes versus those without was higher in males (OR=1.9 versus OR=1.3 in females) [21]. The differential strength and direction of the associations between depression and diabetes in men versus women reported in the current series of thesis studies may therefore be indicative of a methodological issue in the wider literature. A nonsignificant relationship between depression and diabetes onset in women could imply these effects have masked a true association in the literature (in studies reporting aggregated effects), in accordance with Simpson’s Paradox. Simpson's

paradox is a well-known statistical phenomenon which describes a reversal in the relationship between two variables after a third variable is introduced, or alternately describes a scenario in which the relationship between two variables differs within subgroups of a third variable, compared to the observed relationship in the aggregated data [22]. We propose that many of the studies conducted to date which have reported aggregated effects and non-significant associations are vulnerable to effects of this phenomenon, and may not be accurately capturing the true risk of diabetes associated with psychological factors in men and women, respectively.

7.2.2 Differentiating between and controlling for symptoms of anxiety and depression

The meta-analysis presented in Chapter 2 indicates that, although concurrent depression-anxiety represents the most common presentation of either disorder, the literature remains dominated by studies of depression. Furthermore, while the existing handful of studies of anxiety and diabetes tend to attempt to control for depression symptoms, the reverse does not appear to be true. Differential associations between depression, anxiety and diabetes outcomes were observed in all four thesis studies to some extent (especially with respect to sex, as discussed above). The overwhelming focus on depression and the neglect of anxiety disorders may lead to a possible distortion of the evidence in this area, as well as a lack of data on comorbidities involving anxiety.

As mentioned in Chapter 1, major depression and generalized anxiety disorder consist of both overlapping and unique symptoms. We may consider the effects of not controlling for the distinct and overlapping symptoms of depression and anxiety in turn. First, there is evidence that specific symptoms of depression only, and not anxiety, are associated with diabetes outcomes. For example, a study by Khambaty and colleagues indicates that the somatic-vegetative cluster of

symptoms may be largely responsible for the prospective link between depression and insulin resistance, whereas neither the total depression score nor cognitive-affective depression symptoms predict insulin resistance [23]. In addition, neither symptoms of anxiety nor hostility were found to predict insulin changes in the same study [23]. Further research similarly indicates that the association between depression and diagnosed diabetes is primarily driven by somatic-affective, and not cognitive-affective depressive symptoms [24]. One theory behind these associations is that the somatic symptoms associated with depression (e.g., fatigue, hypersomnia, appetite changes) may contribute more to deleterious lifestyle changes such as physical inactivity and high-calorie diets, and subsequent diabetogenic processes, than do the cognitive symptoms (e.g., inability to concentrate, indecisiveness, adhedonia) [23]; likewise, the physical symptoms of anxiety (e.g., restlessness, muscle tension) may be less implicated in these processes or may exert opposite effects. In addition, the cognitive symptoms of anxiety (e.g., excessive worry) may not confer the same risk or even lead to health promoting behaviours with respect to diet and exercise.

As demonstrated by previous research, anxiety appears to have U-shaped relationships with mortality [25], body mass index [26], and blood pressure [27], with a moderate amount of anxious symptoms being associated with the healthiest outcomes. Most of the latter research does not report sex-based results, however, so it is unclear whether these effects would hold equally true for men and women. Regardless, the prototypical behavioural and psychological components of depression and anxiety appear to covary with aspects of diabetes management. This is further evidenced by studies that show that patients with diagnosed depression are more likely to avoid consulting with a health care provider for treatment than those with generalized anxiety disorder [28]. Other research, including the present thesis, has found that depressive symptoms but not anxiety are

associated with glucose metabolism within the same diabetic sample [29]. Previous research, in addition to the present thesis, also suggests differences in inflammation between depression and generalized anxiety disorder; while depression is associated with elevated levels of CRP over time, the association between generalized anxiety and CRP may be completely attenuated by body mass and other factors [30]. Depressed patients with comorbid anxiety have also been found to demonstrate an exaggerated HPA-axis response to a stressor, one that is not observed in depressed patients alone [31]. The consequences of failing to measure or control for the distinct symptoms of anxiety in studies of depression and diabetes outcomes may therefore be to ignore these conflicting influences, and to either inflate or attenuate this relationship toward the null.

Second, we consider the overlapping symptoms of depression and anxiety, which include insomnia, fatigue, loss of concentration, and psychomotor agitation. It is possible that these shared symptoms may be present in many individuals who meet the criteria for an anxiety disorder, but not for major depression. If one or more shared symptoms are associated with diabetes outcomes, the consequence of considering only depressed individuals in research studies would be to misclassify anxious individuals as unexposed when, in fact, they have been exposed to the relevant factor(s). This may lead to an increase in the observed association between the unexposed group and diabetes outcomes, and a decrease in the association between the exposed group and the same outcomes. The overall effect of failing to measure overlapping symptoms of depression and anxiety in anxious individuals would therefore be to bias these associations towards the null.

Generalized anxiety is commonly believed to precede major depression in sequential order [32]. Patients in the general population with comorbid anxiety disorders tend to be younger at the time

of their index episode, and to have earlier onset major depression than those with major depression alone [33]. In diabetic populations, higher levels of baseline anxiety were demonstrated in one study to increase the risk of incident major depression developing during a 2-year follow up [34]. The authors concluded that baseline levels of anxiety might be taken into account in the prevention of major depression in diabetic patients [34]. The exclusion or neglect of individuals with anxiety symptoms in diabetes research may therefore result in missed opportunities to explore earlier options for mental health interventions in these individuals. Interestingly, previous research shows that while anxiety and depression and correlated among outpatients with Type 2 diabetes, this association becomes progressively weaker with increasing age [35]. This could also mean that the above issues may be more relevant in younger age groups.

7.2.3 Study-specific considerations

Population impact of depression and anxiety on Type 2 diabetes incidence: The results of the study in Chapter 4 suggest that while depression and anxiety contribute to diabetes incidence, they do so only in conjunction with metabolic and behavioural factors. Men appear to be particularly vulnerable to the effects of smoking and physical inactivity with respect to diabetes onset. In women, all incident cases were attributable to the presence of the metabolic syndrome, either alone or in conjunction with other risk factors. It is worth noting that many individuals who did not meet the criteria for the metabolic syndrome still had elevated measurements on the individual clinical factors composing this syndrome (i.e., central obesity, hypertension, high cholesterol, raised triglycerides, or hyperglycemia). The impact of reducing or eliminating all of these individual clinical factors on diabetes incidence was therefore not captured in this study, and would exceed

the population impact reported for the presence of the metabolic syndrome. In order for a PAF to have practical public health value beyond the theoretical, the exposure cut-point should be selected such that the "unexposed" level is realistically attainable, as recommended by Rockhill *et al.* (1998) [36]. The attributable fractions for many chronic diseases are generally only high if the risk factors are defined in such a way that almost the entire population is labelled as exposed. The implication - that virtually everyone in the population will need to be shifted to the lowest exposure category to achieve the estimated reduction in burden - may be unrealistic and is not useful from a policy perspective [36].

In this study sample, defining the cut-off for the unexposed group as the complete absence of any of the individual metabolic syndrome factors was unrealistic for two reasons. First, because the expectation of achieving a population entirely free of obesity, hypertension, high cholesterol, raised triglycerides, or hyperglycemia was both daunting and potentially unfeasible. Second, as the majority of people in this study population had at least one metabolic risk factor present, using this cut-off perfectly predicted almost 100% of incident diabetes cases thus precluding sound statistical analyses. The presence or absence of the metabolic syndrome was therefore chosen as the appropriate counterfactual for this study, and represents a modifiable factor whose exposure could be meaningfully reduced by reducing the prevalence of just one or two of the composite factors.

This study illustrates that depression and anxiety are two of many factors that may cluster in individuals and increase diabetes risk. While not being problematic on their own, they appear to have the potential to amplify risk associated with other factors - for example, by exacerbating

problems of diet quality or smoking practices, or by adding to the endocrinologic responses associated with central obesity, hypertension, and other markers of the metabolic syndrome. It has been suggested that the effect of depression on the risk for diabetes might only be noticeable in those who are already at risk for diabetes (e.g., by worsening glycemic control in those with poor glucose tolerance [37]). Or similarly, while depression may worsen glycemic control in everyone, these deficiencies may only be diabetogenic in individuals already close to the threshold for a diabetes diagnoses [37]. Other research suggests that depression and anxiety may work to amplify the effect of cardiometabolic risk factors for diabetes [38], and that these factors are associated with an accelerated progression to diabetes only in high-risk subpopulations [39]. The latter study specifically found that psychological symptoms predicted diabetes incidence in individuals with advanced prediabetes (OR=2.07), but not in low-risk individuals with prediabetes, or in low- or high-risk individuals with normoglycemia [39]. Our study confirms these theories by illustrating that psychological factors, in the absence of other diabetes risk factors, accounts for a negligible fraction of cases in the general population. This highlights the importance of risk factor clustering in diabetes onset, and the potential benefit of multi-pronged approaches aimed at improving mental health while simultaneously reducing other modifiable factors.

Influence of depression and anxiety on Type 2 diabetes management: While the study presented in Chapter 5 found significant associations between depression and anxiety and a small number of key clinical and behavioural outcomes (i.e., HbA1c and CRP levels, diet adherence, physical activity, and the subjective diabetes experience), it is worth noting that these exposures were not associated with the majority of the outcomes that were studied. No associations were evident between depressive symptoms and central obesity, cholesterol, hypertension, triglycerides, home

monitoring of glucose, or foot checks for ulcers. As outlined in Chapter 1, previous research has demonstrated consistent relationships between depression and obesity [40–42]. This is of particular interest since obesity remains one of the strongest risk factors for diabetes onset, increasing the lifetime risk of diabetes by almost 10-fold in some studies [43]. Although the present study did not find an association between depression and obesity, it included adjustments for many biological measurements that may not have been considered in previous studies on this topic (e.g., HDL cholesterol, systolic BP, triglycerides, CRP and serum glucose). It is possible that these factors could account for much of the variance in the observed relationship between depression and obesity. It is also possible that these biological factors constitute intermediaries between depression and obesity, and including them in the model resulted in some degree of statistical overadjustment. Although many of the selected outcomes were not associated with depression and anxiety, glycemic control represents an extremely important clinical factor in diabetes management, and this factor exhibited strong associations with depression in men. Studies on enhancing care for depression within a collaborative care model for diabetes demonstrate that this intervention improves affective and functional status in patients, but has minimal effects of diabetes-specific outcomes among patients with good glycemic control [44]. Based on these findings, and the results of the present study, it appears that depressed individuals with poor glycemic control represent a group of diabetes patients that may benefit the most from interventions for depression. Further research is needed to examine the benefits of depression treatment for preventing dysglycemia in patients experiencing other self-management issues.

Mortality in Type 2 diabetes comorbid with depression and anxiety: Chapter 6 presented a survival analysis which modelled the risk of death over 18 years by baseline depression, anxiety and

diabetes status. This study found that risks of death were increased in the presence of depression and that symptoms of anxiety attenuated these effects downward, with the highest risk of death observed in diabetic men with depression only. The risk of death reported for the latter group was roughly 2.5 times higher than that observed for non-depressed diabetic men, which is higher than the pooled estimates of the increased mortality risk associated with depression in diabetes reported by three previously published meta-analyses (HR=1.76 [45], 1.50 [7], and 1.49 [5]). This increase could be explained by the exclusion of women and individuals with anxiety from the current estimate, both of which likely attenuated this estimate downwards in the cited literature.

Interestingly, the findings of a very recently published study on the impact of anxiety disorders conducted in a large sample of Taiwanese diabetic patients mirrored those presented here. The 5-year survival rate in this study was found to be higher for diabetic patients with anxiety disorders than those without, and a higher risk of mortality was observed in diabetic patients who were male [46]. Anxiety conferred a lower risk of mortality regardless of diabetes type. A second study conducted in Norway also found that elevated depressive symptoms were associated with excess mortality risk in diabetic individuals, with no significant association was observed with either elevated anxiety symptoms alone or combined depression and anxiety symptoms [47]. Together, these findings parallel the results presented in the current thesis, in that the presence of anxiety appears to be either beneficial or to counteract the adverse health effects of depression in individuals with Type 2 diabetes. As the previous studies both used different tools to capture symptoms of depression and anxiety than the tool used in this thesis, this evidence also increases the robustness of our findings and reduces the chances that these are measurement-specific spurious results.

The mechanisms by which anxiety disorders are related to mortality are still unclear; as mentioned previously, increased vigilance, attention to health status, and more frequent outpatient medical visits have been suggested as possible explanations for these protective effects. Similar reasons have been proposed to explain the observed sex-differences in this association, with women being potentially more willing to identify physical symptoms and seek help for them than men [46]. It is interesting to note that both countries in which this relationship has been observed (i.e., Taiwan and Norway) have universal health care systems in place, each of which are characterized by good accessibility and comprehensive population coverage [48, 49]. This may be an important factor in allowing individuals to translate the cognitive experience of anxiety into behavioural actions with health benefits. Further research into whether the relationship between anxiety and mortality is moderated by health care use (including coverage, access, and economic barriers) may be illuminating, and help to elucidate any potentially direct effects of this disorder on longevity and its relevant interactions with depression.

7.2.4 Association versus causation: Assessment of study findings using Bradford Hill's Criteria

As the first two studies presented concern themselves with the etiology of Type 2 diabetes, they are necessarily attempting to identify the causes of the disease. The use of population attributable fractions, in particular, involves implicit inferences about cause-and-effect. The evidence presented in this thesis is therefore summarized under the major Bradford-Hill criteria for assessing causation below. While these criteria are not a formal test of causation, they can play an important role in inferring the best possible explanation from epidemiological data.

Strength: The measures of effect reported in our studies ranged in size from RR=1.30 for anxiety and RR=1.83 for depression with respect to diabetes onset, to odds ratios ranging between 2.00 to 3.00 for self-management, and hazard ratios between 1.60 to 3.50 for mortality risk. Most of these values also had fairly narrow confidence intervals. While these are considered to be moderate rather than strong associations, in combination with other evidence, they are sufficiently large so as to lend credible support to a cause-and-effect interpretation.

Consistency: Chapter 1 summarized existing evidence from a range of different studies conducted in various settings which examine the effects of depression and anxiety on diabetes outcomes. Overall, the findings of the four thesis studies were largely consistent with those found in the literature. Additionally, we argue that several of the previously observed inconsistencies in the literature may stem from failure to stratify results by sex rather than from true incongruities in these associations.

Temporal Sequence: The longitudinal design of three out of the four studies allowed us to assess temporality and rule out reverse causation in these results. While there is evidence that many of these associations are bidirectional in nature (e.g., diabetes onset leading to depression [51]), the present studies lend support to the theory that the effects on diabetes outcomes manifest themselves only after the cause is observed, for the specific relationships examined here.

Dose-Response Relationship: The present studies used dichotomous exposure variables and did not examine the presence or absence of a dose-response relationship. However, examples of such a relationship have been documented in the wider literature with respect to depression [24, 52]. A linear and consistent relationship has been demonstrated between depression severity and diabetes

prevalence (ranging from 6.9% in minimal depression, 7.6% in mild, 9% in moderate, and 10.5% in severe depression) in a survey of over 15,000 participants [24]. While the evidence for a dose-response relationship between depression severity and diabetes does exist, similar evidence with respect to anxiety is still lacking.

Experimental Evidence: The present studies have not added experimental evidence in support of these associations. It is logistically difficult and ethically inappropriate to randomize participants to receive the psychological exposures in question, hence the reliance on observational studies in this area. However, some experimental evidence does exist in the literature with respect to the treatment of depression and subsequent influences on diabetes outcomes. A meta-analysis of randomized controlled trials of psychological interventions, published in the Lancet in 2004, found moderate improvements in long-term glycemic control in patients with Type 2 diabetes receiving these interventions [53].

Plausibility: Chapter 1 (Section 1.2) outlines in detail a number of plausible biological and behavioural mechanisms through which depression and/or anxiety may influence diabetes onset and clinical management. With respect to mortality, many of the same mechanisms may be at play, with poor clinical management leading to increases in medical complications and decrements in overall health. Less clearly explained by the current literature is the finding that anxiety may offer protective benefits against mortality in certain groups, although it is possible that this may also be mediated by biological factors such as blood pressure [27]. Overall, the evidence for a biologically plausible cause-and-effect relationship between these variables is good.

Coherence of Evidence: The findings of this thesis do not conflict with the larger evidence base, and are compatible with existing theory and knowledge.

Overall, although the above evidence is not uniformly strong across all criteria, a moderate amount of evidence does lend support to the existence of a causal relationship between psychological factors and diabetes outcomes.

7.3 Strengths and Limitations

7.3.1 Strengths

This thesis had several strengths. The use of a large, population-based survey linked to both biobank data and a national mortality registry allowed an examination of several outcomes associated with psychological factors that are not usually possible to study on such a large scale. This also enabled the consideration of a wide range of relevant sociodemographic and clinical covariates in these associations. Recall and reporting biases of the outcome were also minimized due to the prospective nature of the survey, and the use of clinical exams to confirm self-reported diabetes diagnoses allowed diabetes subtypes other than Type 2 to be excluded.

With the exception of the cross-sectional study presented in Chapter 5, the time sequence of events in these studies was clear and mitigated the potential for reverse causation in these associations. The studies also included appropriate follow-up times to assess diabetes incidence and subsequent mortality. Results were stratified by sex and included formal tests of interaction by sex. And lastly, by identifying and adjusting for symptoms of anxiety at the outset, this thesis has controlled for a confounder that has been ubiquitously neglected in the literature to date.

7.3.2 Limitations and methodological considerations

Exposure measurement: As highlighted in the meta-analysis presented in Chapter 2, the strength of the association between depression and diabetes may differ depending on the type of assessment tool used (i.e., self-report versus structured clinical interview). This is supported by previous research, including a meta-analysis of the relationship between depression and insulin resistance,

which found a much greater standardized effect size for studies using diagnostic interviews rather than self-report measures (i.e., 0.46 versus 0.13) [54]. Similarly, a meta-analyses of depression and glycemic control found that depression was significantly associated with hyperglycemia, and the standardized effect size was larger when standardized interviews and diagnostic criteria rather than self-report questionnaires were used to assess depression (i.e., 0.28 versus 0.15) [55]. All three original studies presented in Chapters 4-6 relied on a self-report tool to measure depression and anxiety. While this tool has been evaluated against the HADS and the HSCL, it is unclear whether these findings would replicate using a DSM-based assessment, and there is a possibility that the reported effect sizes in this thesis may be underestimated overall compared to using a clinical diagnosis of either disorder. However, self-report questionnaires have the advantage of capturing sub-threshold symptoms, which have demonstrated associations with clinical diabetes outcomes [56]. These observed differences may therefore be due the inclusion of individuals with less severe but still clinically relevant symptoms, which may provide a better picture of the prevalence and burden associated with the exposure at the community level than more stringent diagnostic criteria might.

In addition, although depression and anxiety are often episodic or chonic in nature, the current studies only included baseline measures of these symptoms. Information on depression or anxiety history was not available, and it was not possible to consider duration of either of these conditions. Periodic assessments of mental health symptoms are likely to capture those with chronically high symptoms disproportionately, as they will be more likely to score above the symptom threshold at each time point, whereas people with episodic or recurrent conditions are more likely to be in remission at time of assessment. This means that some individuals classified as ‘non-exposed’ at

baseline may have mental health histories relevant to diabetes outcomes that were not captured. The overall effect of this omission would likely be to dilute the differences between our two groups, and bias the results towards the null.

A similar potential for the misclassification of diabetes status between study waves exists, as we were unable to exclude cases of prediabetes at baseline. Individuals very close to the threshold of Type 2 diabetes but who were undiagnosed at the beginning of the study may have been classified as diabetes-free, and gone on to develop the disease shortly after the study assessments were performed. This issue specifically applies to the longitudinal study of mortality associated with baseline depression, anxiety, and diabetes presented in Chapter 6. Including individuals with prediabetes in the non-diabetic group would have the effect of artificially increasing the mortality rate in the reference group; again, this omission would likely have the overall effect of biasing the results towards the null.

Covariates: Some of the covariates included in these analyses were dichotomized, rather than included as continuous variables or as multiple categories. In some instances, this was because the HUNT survey collected broadly categorized information (e.g., physical activity); in others, this was done to simplify interpretation (e.g., as for the population attributable fractions for diabetes associated with smoking or the metabolic syndrome in Chapter 4), and to keep the focus on clinically significant cut-points, due to their ease of interpretation and relevance to clinicians and patients. Operationalizing variables this way may be associated with a loss of data or an oversimplification of these relationships. However, in cases where the data were available, we performed sensitivity analyses around more precise measures of specific covariates (e.g., smoking

as a continuous variable reflecting pack-years smoked rather than current smoking status, or a continuous measure of waist circumference rather than a clinical cut-point). The estimates of main effects appeared to be consistently unchanged when covariates were operationalized as dichotomous versus continuous (data not shown), and the potential loss of precision in these variables is therefore not expected to impact the findings of this thesis overall.

Many of the above covariates may also be important intermediaries of the relationship between depression, anxiety, and diabetes, as described in Chapter 1. While these variables were included in statistical models in an attempt to estimate the independent association between psychological exposures and diabetes outcomes, while holding all other factors constant, these variables have the potential to meet the criteria for both confounding and mediating variables. The act of controlling for mediating variables may result in overadjustment bias, as described by Rothman, Greenland and Lash [57]. This is of concern in scenarios where depression or anxiety precede and precipitate the emergence of other risk factors for diabetes, and controlling for these intermediary factors may overlook the full influence of psychological exposures on diabetogenic processes. Overadjustment in the context of intermediate variables is generally proven to bias results towards the null. It is therefore possible that we have underestimated the contributions of depression and anxiety in the current studies, and the estimates presented here may be considered conservative in this regard.

Generalizability: Many efforts have been made to examine the representativeness and generalizability of the HUNT Study with respect to the wider Norwegian population [58]. Although the level of education and income in Nord-Trøndelag County fall slightly below the national average, the mortality and health status of individuals in the region are found to be

representative of the rest of Norway [59]. The findings of the three thesis studies using HUNT data should therefore generalize well within a Norwegian context. However, due to the very low ethnic heterogeneity of the study population (less than 3% non-Caucasian), these findings might not generalize well to other countries, particularly in North America or lower income countries. Ethnicity, especially minority status, is strongly associated with diabetes outcomes in Western countries [60, 61]. Diabetes prevalence, glycemic control, and diabetes complications have all been demonstrated to be worse in specific ethnic groups such as Hispanic or Indigenous communities [62, 63], and these groups simultaneously face a higher burden of depression [64]. It is therefore uncertain whether the strength of the associations observed between these factors in the present studies would be consistently observed in more ethnically heterogenous populations.

In addition to the preceding methodological limitations, there always exists the possibility that the results generated in each individual thesis study were due to the presence of bias, confounding, or chance. Bias due to attrition, for example, is a form of selection bias that may be particularly problematic in large observational cohort studies. While participation rates in epidemiological studies appear to be declining in recent decades [65], a systematic review found that only about 10% of the articles published in a given journal include demographic analyses of participants and non-participants [66]. However, non-participation in the HUNT Study has been evaluated and explored in several papers [59, 67–70], particularly with respect to health status between participants and non-participants. Attrition in HUNT 2 has been associated with high levels of mental distress (OR=1.84)[69], as well as obesity, hypertension, and less education [70]; similarly, attrition in HUNT 3 has been associated with socioeconomic status, chronic illnesses and survival [59]. The influence of nonparticipation on the current thesis findings may therefore lead to

underestimates of the prevalence of diabetes, depression and anxiety. It may also lead to underestimates of these associations if the most severely impaired (and likely comorbid) individuals are disproportionately absent from the respective study samples. This may introduce a differential bias into all three thesis studies using HUNT data, attenuating the estimates of effect in these studies towards the null.

It has also been suggested that the increased prevalence of depression observed in Type 2 diabetes may be an artifact of detection bias; that is, the possibility that depression is more likely to be diagnosed in diabetic patients simply as a result of them seeking more frequent medical care. As the present thesis uses a population-based survey to assess psychological symptoms, and was not dependent on an assessment of depression or anxiety made by contact with a healthcare provider or the use of administrative data, we can refute detection bias as a potential explanation.

The present studies are susceptible to the presence of unmeasured confounders, that may either account for or obscure true associations. An important known confounder that was absent from the study presented in Chapter 5 was education. While data on education level was collected in HUNT 2, it was unfortunately not collected in HUNT 3. This was due to an expectation by the survey implementers that the data would be subsequently linked with the national education registry, for which permission was not ultimately granted. Based on the available data for HUNT 2, while 30% of non-diabetic individuals had received some form of post-secondary education, only 9.5% of individuals with Type 2 diabetes had. Low educational attainment was therefore more common in individuals with Type 2 diabetes in the HUNT 2 study population. Education appears to be an important moderator of these relationships, with multiple studies showing the risk

of diabetes onset following baseline depression is markedly higher in individuals with less than a high school education [71, 72]. It is therefore possible that education could attenuate the relationship between affective symptoms and the specific diabetes outcomes presented in this paper. These estimates would likely be underestimated in those with low educational attainment and overestimated in those with high educational attainment. However, we expect that less than 10% of the HUNT 3 study population in question would have received a post-secondary education, and that the overall findings presented in Chapter 5 would not change considerably.

And finally, there is the possibility that some of the statistical findings presented here were spurious or due to chance. Although more than one outcome was tested in each study, we did not undertake any formal corrections for multiple hypothesis testing (e.g., a Bonferroni or Benamini-Hochberg correction). Corrections for multiple comparisons are generally recommended when the outcomes in question are determined to be independent or weakly correlated with another [73]. With respect to the outcomes in this thesis, many of the measures (e.g., clinical measures such as HbA1c, triglycerides, cholesterol, or blood pressure) were too highly correlated to justify a p-value adjustment. Many of the behavioural and self-management diabetes measures in our study are also correlated with each other, as well as with the other clinical measures. While these study outcomes did not meet the assumptions required to perform standard adjustments for multiple testing, most of the results in question yielded p-values between $p<0.01$ and $p<0.001$, and would likely have survived correction.

7.4 Future Directions

The preceding sections highlight the current thesis findings that diabetes outcomes varied noticeably with respect to two important factors: sex and affective symptom type. As these associations may heavily depend on specific symptoms, subtypes or phenotypes, as well as patient sex, further research is needed that examines sex-related differences in the clinical features of depression and anxiety in diabetic individuals. Given the consistently high correlation observed between these disorders, critics have questioned the validity of categorical diagnostic classifications of depression and anxiety, and have suggested that a dimensional approach may be more appropriate [74–76]. Because of the heterogenous (and sometimes opposing) nature of the symptoms composing these disorders, the exploration of symptom-specific associations with diabetes outcomes may also be a useful parallel avenue of investigation. A brief *post-hoc* analysis using the current HUNT 2 dataset demonstrated highly significant associations between many individual symptoms of depression and anxiety and both diabetes onset and mortality (data not shown). Studies investigating associations between diabetes and the individual symptoms or domains of depression (e.g., somatic or cognitive) are rare [24], and such studies appear to be non-existent for anxiety. The interpretation of associations between individual symptoms or domains and diabetes outcomes might be more straightforward than those put forward at the disorder level. Furthermore, it is possible that certain subgroups of symptoms tend to occur more frequently in either men or women. Future research should therefore aim to examine the relationships between depression, anxiety and diabetes outcomes with finer granularity, within men and women respectively.

As previously mentioned, most of the results of the current thesis studies were obtained using a Norwegian general population sample, and may not generalize to different ethnic groups. The prevalence of Type 2 diabetes is increasing disproportionately in non-Caucasian populations globally [77], and a growing number of studies indicate the importance of race on diabetes outcomes [78, 79], depression and anxiety outcomes [80], and the psychopharmacologic management of these disorders [80, 81]. Prior to arriving at similar conclusions to those drawn here, further research is needed that examines psychological comorbidities in diabetes within both Western ethnic minority groups and across the general populations of developing countries.

As further described in the Limitations section, the chronic and episodic nature of depression and anxiety suggest that an examination of trajectories of these symptoms may be more informative than baseline assessments. Trajectory analyses could be used in future research in order to document the longitudinal effects of depression and anxiety on diabetes outcomes, and test questions about individual differences in stability and change of psychological symptoms over time [82]. Such research would benefit by examining depression and anxiety status prior to diabetes onset, and at multiple time points during the course of the disease. We currently know very little about which individuals are more vulnerable to depression onset prior to receiving a diabetes diagnoses versus post-diagnoses based on baseline characteristics; and, whether it is possible to differentiate between groups of individuals at baseline who will fare more poorly or experience improved outcomes during the course of the disease.

The use of a life course approach (i.e., a multidisciplinary approach to understand the importance of time and timing in epidemiological associations [83]) may provide the most appropriate

framework for future research in this area. Although life course approaches have been applied to the study of both depression and diabetes individually, they have rarely been used to study their comorbidity. A recent study of a large sample of primary care patients with chronic conditions demonstrated that the majority (72.6%) had two or more concurrent conditions [84], and a systematic review of empirical studies on comorbidity and multimorbidity found depression to be the disease that was most commonly clustered with other conditions, followed by diabetes and hypertension [85]. Multimorbidity is a concept of growing importance in public health, and any efforts to better understand its occurrence would therefore be of wide interest. As most clinical guidelines address single diseases, the treatment of patients with multiple conditions remains a major challenge. The identification of early life risk factors associated with the development of psychological and medical comorbidities may therefore constitute a valuable scientific contribution, given that many of the shared risks for depression and diabetes begin much earlier in life (e.g., in utero[86, 87]).

Life course approaches may also help to address the particular issue of the earlier age of onset for depression and anxiety as an explanation for the observed associations [10]. The median age of onset for depression and anxiety is 23-30 years [88], with anxiety disorders emerging prior to adulthood in many individuals [89], while the average age of onset for diabetes is closer to 50 years [90]. The consistently reported observation of a stronger effect for depression preceding diabetes than for the reverse association could therefore be an artifact of the combined natural history of these diseases. An examination of sensitive periods throughout the life course for the emergence of these comorbidities may therefore prove enlightening. While the majority of adults with diabetes in developed countries are aged 65 or over, the age of onset in developing countries

is much younger, with the majority of individuals between 45-64 years old. This may result in an increased prevalence of these comorbidities in developing countries, and similar life course research in this context could yield informative findings.

A further use of the life-course approach would be to better understand the function of endogenous sex-hormones (i.e., androgens and estrogens) in the development of depression, anxiety and diabetes and their subsequent comorbidities, especially in women. Research to date has not yet identified a subgroup of women with psychological symptoms that are more vulnerable to diabetes onset, but the evidence reviewed in this thesis points to the possible existence of a small high-risk group. The longitudinal interplay between endogenous hormones and vulnerabilities to depression, anxiety, and diabetes is an understudied area that may hold the key to explaining everything from the respective timings of disease onset to the emergence of these comorbidities, as described above.

7.5 Conclusions

At a macro level, this thesis points to the potential of depression and anxiety to impact each key stage of the diabetes experience, with pronounced effects on diabetes onset and mortality. While depression and anxiety alone do not represent important risks for diabetes onset, they are associated with substantial increases in diabetes risk in combination with traditional risk factors. Differential associations appear to exist between symptoms of depression and anxiety with respect to diabetes outcomes, and their co-occurrence is not associated with demonstrably poorer outcomes (possibly as a result of this heterogeneity). The current findings highlight the importance of controlling for symptoms of anxiety in studies of depression. The bulk of literature in this area to date presents a simple summary estimate for both men and women; however, the findings of this body of work suggest that sex is an important effect modifier of the relationship between psychological risk factors and diabetes outcomes. Further research is needed to disentangle the complex mediational relationships that may influence the clinical management of diabetes in the presence of psychological comorbidities. In addition, future research should attempt to use life course approaches to explore interactions between psychological and traditional risk factors for diabetes in more detail, paying specific attention to sex-based differences in these associations.

REFERENCES

1. Knol MJ, Twisk JWR, Beekman ATF, et al (2006) Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. Diabetologia 49:837–845. doi: 10.1007/s00125-006-0159-x

2. Cosgrove MP, Sargeant LA, Griffin SJ (2008) Does depression increase the risk of developing type 2 diabetes? Occup Med (Chic Ill) 58:7–14. doi: 10.1093/occmed/kqm105

3. Mezuk B, Eaton W, Albrecht S, Golden S (2008) Depression and type 2 diabetes over the lifespan a meta-analysis. Diabetes Care

4. Hasan SS, Clavarino AM, Mamun AA, et al (2013) Population impact of depression either as a risk factor or consequence of type 2 diabetes in adults: A meta-analysis of longitudinal studies. Asian J Psychiatr 6:460–472. doi: 10.1016/j.ajp.2013.09.008

5. van Dooren FEP, Nefs G, Schram MT, et al (2013) Depression and risk of mortality in people with diabetes mellitus: a systematic review and meta-analysis. PLoS One 8:e57058. doi: 10.1371/journal.pone.0057058

6. Hofmann M, Köhler B, Leichsenring F, Kruse J (2013) Depression as a risk factor for mortality in individuals with diabetes: a meta-analysis of prospective studies. PLoS One 8:e79809. doi: 10.1371/journal.pone.0079809

7. Park M, Katon WJ, Wolf FM (2013) Depression and risk of mortality in individuals with diabetes: a meta-analysis and systematic review. Gen Hosp Psychiatry 35:217–25. doi: 10.1016/j.genhosppsych.2013.01.006

8. Demmer RT, Gelb S, Suglia SF, et al (2015) Sex differences in the association between depression, anxiety, and type 2 diabetes mellitus. Psychosom Med 77:467–77. doi: 10.1097/PSY.0000000000000169

9. Kautzky-Willer A, Harreiter J, Pacini G (2016) Sex and Gender Differences in Risk, Pathophysiology and Complications of Type 2 Diabetes Mellitus. Endocr Rev 37:278–316. doi: 10.1210/er.2015-1137

10. Saydah SH, Brancati FL, Golden SH, et al (2003) Depressive symptoms and the risk of type 2 diabetes mellitus in a US sample. Diabetes Metab Res Rev 19:202–208. doi: 10.1002/dmrr.353

11. Golden SH, Lazo M, Carnethon M, et al (2008) Examining a Bidirectional Association Between Depressive Symptoms and Diabetes. JAMA 299:2751. doi: 10.1001/jama.299.23.2751

12. Gangwisch JE, Gross R, Malaspina D (2015) Differential Associations Between Depression, Risk Factors for Insulin Resistance and Diabetes Incidence in a Large U.S. Sample. Isr J Psychiatry Relat Sci 52:85–90.

13. Angst J, Gamma A, Gastpar M, et al (2002) Gender differences in depression. Eur Arch Psychiatry Clin Neurosci 252:201–209. doi: 10.1007/s00406-002-0381-6

14. Kessler RC (2003) Epidemiology of women and depression. J Affect Disord 74:5–13.

15. Sopjani I, Vehapi S, Gorani D, et al The Relation Between Depressive Symptoms and Self-Care in Patients with Diabetes Mellitus Type 2 in Kosovo. doi: 10.5455/medarh.2016.70.425-428

16. McLean CP, Asnaani A, Litz BT, Hofmann SG (2011) Gender differences in anxiety disorders: prevalence, course of illness, comorbidity and burden of illness. J Psychiatr Res 45:1027–35. doi: 10.1016/j.jpsychires.2011.03.006

17. Suglia SF, Demmer RT, Wahi R, et al (2016) Depressive Symptoms During Adolescence and Young Adulthood and the Development of Type 2 Diabetes Mellitus. Am J Epidemiol 183:269–276. doi: 10.1093/aje/kwv149

18. Zitzmann M (2006) Testosterone and the brain. Aging Male 9:195–199. doi: 10.1080/13685530601040679

19. Rohr UD (2002) The impact of testosterone imbalance on depression and women's health. Maturitas 41 Suppl 1:S25-46.

20. Ding EL, Song Y, Malik VS, Liu S (2006) Sex Differences of Endogenous Sex Hormones and Risk of Type 2 Diabetes. JAMA 295:1288. doi: 10.1001/jama.295.11.1288

21. Ali S, Stone MA, Peters JL, et al (2006) The prevalence of co-morbid depression in adults with Type 2 diabetes: a systematic review and meta-analysis. Diabet Med 23:1165–1173. doi: 10.1111/j.1464-5491.2006.01943.x

22. Tu Y-K, Gunnell D, Gilthorpe MS (2008) Simpson's Paradox, Lord's Paradox, and Suppression Effects are the same phenomenon--the reversal paradox. Emerg Themes Epidemiol 5:2. doi: 10.1186/1742-7622-5-2

23. Khambaty T, Stewart JC, Muldoon MF, Kamarck TW (2014) Depressive symptom clusters as predictors of 6-year increases in insulin resistance: data from the Pittsburgh Healthy Heart Project. Psychosom Med 76:363–9. doi: 10.1097/PSY.0000000000000063

24. Wiltink J, Michal M, Wild PS, et al (2014) Associations between Depression and Diabetes in the Community: Do Symptom Dimensions Matter? Results from the Gutenberg Health Study. PLoS One 9:e105499. doi: 10.1371/journal.pone.0105499

25. Mykletun A, Bjerkeset O, Overland S, et al (2009) Levels of anxiety and depression as predictors of mortality: the HUNT study. Br J Psychiatry 195:118–25. doi: 10.1192/bjp.bp.108.054866

26. Haghighi M, Jahangard L, Ahmadpanah M, et al (2016) The relation between anxiety and BMI – is it all in our curves? Psychiatry Res 235:49–54. doi: 10.1016/j.psychres.2015.12.002

27. Davies SJC, Bjerkeset O, Nutt DJ, Lewis G (2012) A U-shaped relationship between systolic blood pressure and panic symptoms: the HUNT study. Psychol Med 42:1969–1976. doi: 10.1017/S0033291711003047

28. Andrews G, Sanderson K, Slade T, Issakidis C (2000) Why does the burden of disease persist? Relating the burden of anxiety and depression to effectiveness of treatment. Bull World Health Organ 78:446–454. doi: 10.1590/s0042-96862000000400006

29. Bouwman V, Adriaanse MC, van 't Riet E, et al (2010) Depression, Anxiety and Glucose Metabolism in the General Dutch Population: The New Hoorn Study. PLoS One 5:e9971. doi: 10.1371/journal.pone.0009971

30. Copeland WE, Shanahan L, Worthman C, et al (2012) Generalized anxiety and C-reactive protein levels: a prospective, longitudinal analysis. Psychol Med 42:2641–2650. doi: 10.1017/S0033291712000554

31. Young EA, Abelson JL, Cameron OG (2004) Effect of comorbid anxiety disorders on the Hypothalamic-Pituitary-Adrenal axis response to a social stressor in major depression. Biol Psychiatry 56:113–120. doi: 10.1016/j.biopsych.2004.03.017

32. Moffitt TE, Harrington H, Caspi A, et al (2007) Depression and Generalized Anxiety Disorder. Arch Gen Psychiatry 64:651. doi: 10.1001/archpsyc.64.6.651

33. Fava M, Rankin MA, Wright EC, et al Anxiety disorders in major depression. Compr Psychiatry 41:97–102.

34. Bot M, Pouwer F, Ormel J, et al (2010) Predictors of incident major depression in diabetic outpatients with subthreshold depression. Diabet Med 27:1295–1301. doi: 10.1111/j.1464-5491.2010.03119.x

35. Trento M, Raballo M, Trevisan M, et al (2012) A cross-sectional survey of depression, anxiety, and cognitive function in patients with type 2 diabetes. Acta Diabetol 49:199–203. doi: 10.1007/s00592-011-0275-z

36. Rockhill B, Newman B, Weinberg C (1998) Use and misuse of population attributable fractions. Am J Public Health 88:15–9.

37. Rubin RR, Peyrot M (2002) Was Willis right? Thoughts on the interaction of depression and diabetes. Diabetes Metab Res Rev 18:173–175. doi: 10.1002/dmrr.292

38. Deschênes SS, Burns RJ, Graham E, Schmitz N (2016) Prediabetes, depressive and anxiety symptoms, and risk of type 2 diabetes: A community-based cohort study. J Psychosom Res 89:85–90. doi: 10.1016/j.jpsychores.2016.08.011

39. Virtanen M, Ferrie JE, Tabak AG, et al (2014) Psychological Distress and Incidence of Type 2 Diabetes in High-Risk and Low-Risk Populations: The Whitehall II Cohort Study. Diabetes Care 37:2091–2097. doi: 10.2337/dc13-2725

40. Luppino FS, de Wit LM, Bouvy PF, et al (2010) Overweight, obesity, and depression: a

systematic review and meta-analysis of longitudinal studies. Arch Gen Psychiatry 67:220–9. doi: 10.1001/archgenpsychiatry.2010.2

41. Labad J, Price JF, Strachan MWJ, et al (2010) Symptoms of depression but not anxiety are associated with central obesity and cardiovascular disease in people with type 2 diabetes: the Edinburgh Type 2 Diabetes Study. Diabetologia 53:467–71. doi: 10.1007/s00125-009-1628-9

42. de Wit LM, van Straten A, van Herten M, et al (2009) Depression and body mass index, a u-shaped association. BMC Public Health 9:14. doi: 10.1186/1471-2458-9-14

43. Narayan KM V, Boyle JP, Thompson TJ, et al (2007) Effect of BMI on lifetime risk for diabetes in the U.S. Diabetes Care 30:1562–6. doi: 10.2337/dc06-2544

44. Williams JW, Katon W, Lin EHB, et al (2004) The effectiveness of depression care management on diabetes-related outcomes in older patients. Ann Intern Med 140:1015–1024.

45. Hofmann M, Köhler B, Leichsenring F, Kruse J (2013) Depression as a Risk Factor for Mortality in Individuals with Diabetes: A Meta-Analysis of Prospective Studies. PLoS One 8:e79809. doi: 10.1371/journal.pone.0079809

46. Huang C-J, Hsieh H-M, Chiu H-C, et al (2017) Impact of Anxiety Disorders on Mortality for Persons With Diabetes: A National Population-Based Cohort Study. Psychosomatics 58:266–273. doi: 10.1016/j.psym.2016.11.009

47. Iversen MM, Nefs G, Tell GS, et al (2016) Anxiety and Depressive Symptoms as Predictors of All-Cause Mortality among People with Insulin-Naïve Type 2 Diabetes: 17-Year Follow-Up of the Second Nord-Trøndelag Health Survey (HUNT2), Norway. PLoS One 11:e0160861. doi: 10.1371/journal.pone.0160861

48. Wu T-Y, Majeed A, Kuo KN (2010) An overview of the healthcare system in Taiwan. London J Prim Care (Abingdon) 3:115–9.

49. Lindahl A, Squires D (2016) The Norwegian Health Care System. Int Profiles Heal Care Syst 92–98.

50. Elderon L, Whooley MA (2013) Depression and Cardiovascular Disease. Prog Cardiovasc Dis 55:511–523. doi: 10.1016/j.pcad.2013.03.010

51. Golden SH, Lazo M, Carnethon M, et al (2008) Examining a bidirectional association between depressive symptoms and diabetes. Jama J Am Med Assoc 299:2751–2759.

52. Black S, Markides K, Ray L (2003) Depression predicts increased incidence of adverse health outcomes in older Mexican Americans with type 2 diabetes. Diabetes Care

53. Ismail K, Winkley K, Rabe-Hesketh S, et al (2004) Systematic review and meta-analysis of randomised controlled trials of psychological interventions to improve glycaemic control in patients with type 2 diabetes. Lancet (London, England) 363:1589–97.

54. Kan C, Silva N, Golden SH, et al (2013) A systematic review and meta-analysis of the association between depression and insulin resistance. Diabetes Care 36:480–9. doi: 10.2337/dc12-1442

55. Lustman PJ, Anderson RJ, Freedland KE, et al (2000) Depression and Poor Glycemic Control: A meta-analytic review of the literature. Diabetes Care 23:934–942.

56. Schmitz N, Gariépy G, Smith KJ, et al (2014) Recurrent subthreshold depression in type 2 diabetes: an important risk factor for poor health outcomes. Diabetes Care 37:970–8. doi: 10.2337/dc13-1832

57. Rothman KJ, Greenland S, Lash TL (2008) Modern epidemiology. Wolters Kluwer Health/Lippincott Williams & Wilkins

58. Krokstad S, Langhammer A, Hveem K, et al (2013) Cohort Profile: the HUNT Study, Norway. Int J Epidemiol 42:968–77. doi: 10.1093/ije/dys095

59. Langhammer A, Krokstad S, Romundstad P, et al (2012) The HUNT study: participation is associated with survival and depends on socioeconomic status, diseases and symptoms. BMC Med Res Methodol 12:143. doi: 10.1186/1471-2288-12-143

60. Narayan KMV, Boyle JP, Thompson TJ, et al (2003) Lifetime Risk for Diabetes Mellitus in the United States. JAMA 290:1884. doi: 10.1001/jama.290.14.1884

61. Shai I, Jiang R, Manson JE, et al (2006) Ethnicity, obesity, and risk of type 2 diabetes in women: a 20-year follow-up study. Diabetes Care 29:1585–90. doi: 10.2337/dc06-0057

62. Ell K, Katon W, Cabassa LJ, et al (2009) Depression and diabetes among low-income Hispanics: design elements of a socioculturally adapted collaborative care model randomized controlled trial. Int J Psychiatry Med 39:113–32. doi: 10.2190/PM.39.2.a

63. Dyck R, Osgood N, Lin TH, et al (2010) Epidemiology of diabetes mellitus among First Nations and non-First Nations adults. Can Med Assoc J 182:249–56. doi: 10.1503/cmaj.090846

64. Dunlop DD, Song J, Lyons JS, et al (2003) Racial/ethnic differences in rates of depression among preretirement adults. Am J Public Health 93:1945–52.

65. Morton LM, Cahill J, Hartge P (2006) Reporting Participation in Epidemiologic Studies: A Survey of Practice. Am J Epidemiol 163:197–203. doi: 10.1093/aje/kwj036

66. Demark-Wahnefried W, Bowen DJ, Jabson JM, Paskett ED (2011) Scientific Bias Arising from Sampling, Selective Recruitment, and Attrition: The Case for Improved Reporting. Cancer Epidemiol Biomarkers Prev 20:415–418. doi: 10.1158/1055-9965.EPI-10-1169

67. Holmen J, Midthjell K, Krüger Ø, et al (2003) The Nord-Trøndelag Health Study 1995-97 (HUNT 2): Objectives, contents, methods and participation. Nor Epidemiol 13:19–32.

68. Holmen J, Midthjell K, Forsén L, et al (1990) A health survey in Nord-Trøndelag 1984-86. Participation and comparison of attendants and non-attendants. Tidsskr Nor

Laegeforen 110:1973–7.

69. Torvik FA, Rognmo K, Tambs K (2012) Alcohol use and mental distress as predictors of non-response in a general population health survey: the HUNT study. Soc Psychiatry Psychiatr Epidemiol 47:805–816. doi: 10.1007/s00127-011-0387-3

70. Honningsvåg L-M, Linde M, Håberg A, et al (2012) Does health differ between participants and non-participants in the MRI-HUNT study, a population based neuroimaging study? The Nord-Trøndelag health studies 1984-2009. BMC Med Imaging 12:23. doi: 10.1186/1471-2342-12-23

71. Carnethon MR, Kinder LS, Fair JM, et al (2003) Symptoms of Depression as a Risk Factor for Incident Diabetes: Findings from the National Health and Nutrition Examination Epidemiologic Follow-up Study, 1971-1992. Am J Epidemiol 158:416–423. doi: 10.1093/aje/kwg172

72. Mezuk B, Eaton WW, Golden SH, Ding Y (2008) The influence of educational attainment on depression and risk of type 2 diabetes. Am J Public Health 98:1480–5. doi: 10.2105/AJPH.2007.126441

73. Shi Q, Pavey ES, Carter RE (2012) Bonferroni-based correction factor for multiple, correlated endpoints. Pharm Stat 11:300–309. doi: 10.1002/pst.1514

74. Goldberg DP, Huxley P (1992) Common mental disorders : a bio-social model. Tavistock/Routledge

75. Goldberg D (1994) A bio-social model for common mental disorders. Acta Psychiatr Scand Suppl 385:66–70.

76. Beekman ATF, de Beurs E, van Balkom AJLM, et al (2000) Anxiety and Depression in Later Life: Co-Occurrence and Communality of Risk Factors. Am J Psychiatry 157:89–95. doi: 10.1176/ajp.157.1.89

77. International Diabetes Federation (2015) IDF Diabetes Atlas, 7th Edition. International Diabetes Federation, Brussels, Belgium

78. Link CL, McKinlay JB (2009) Disparities in the prevalence of diabetes: is it race/ethnicity or socioeconomic status? Results from the Boston Area Community Health (BACH) survey. Ethn Dis 19:288–92.

79. Karter AJ, Ferrara A, Liu JY, et al (2002) Ethnic Disparities in Diabetic Complications in an Insured Population. JAMA 287:2519. doi: 10.1001/jama.287.19.2519

80. Schraufnagel TJ, Wagner AW, Miranda J, Roy-Byrne PP (2008) Treating Minority Patients With Depression and Anxiety: What Does the Evidence Tell Us? Focus J Lifelong Learn Psychiatry 6:517–527. doi: 10.1176/foc.6.4.foc517

81. Lin KM (2001) Biological differences in depression and anxiety across races and ethnic groups. J Clin Psychiatry 62 Suppl 13:13-9–1.

82. Curran PJ, Hussong AM (2003) The use of latent trajectory models in psychopathology research. J Abnorm Psychol 112:526–44. doi: 10.1037/0021-843X.112.4.526

83. Lynch J, Smith GD (2005) A Life Course Approach to Chronic Disease Epidemiology. Annu Rev Public Health 26:1–35. doi: 10.1146/annurev.publhealth.26.021304.144505

84. Pengpid S, Peltzer K (2017) Multimorbidity in Chronic Conditions: Public Primary Care Patients in Four Greater Mekong Countries. Int J Environ Res Public Health 14:1019. doi: 10.3390/ijerph14091019

85. Sinnige J, Braspenning J, Schellevis F, et al (2013) The Prevalence of Disease Clusters in Older Adults with Multiple Chronic Diseases – A Systematic Literature Review. PLoS One 8:e79641. doi: 10.1371/journal.pone.0079641

86. Costello EJ, Worthman C, Erkanli A, Angold A (2007) Prediction From Low Birth Weight to Female Adolescent Depression. Arch Gen Psychiatry 64:338. doi: 10.1001/archpsyc.64.3.338

87. Whincup PH, Kaye SJ, Owen CG, et al (2008) Birth Weight and Risk of Type 2 Diabetes. JAMA 300:2886. doi: 10.1001/jama.2008.886

88. Goodwin GM (2015) The overlap between anxiety, depression, and obsessive-compulsive disorder. Dialogues Clin Neurosci 17:249–60.

89. Hudson JL (2017) Prevention of Anxiety Disorders Across the Lifespan. JAMA Psychiatry. doi: 10.1001/jamapsychiatry.2017.2430

90. Koopman RJ, Mainous AG, Diaz VA, et al (2005) Changes in age at diagnosis of type 2 diabetes mellitus in the United States, 1988 to 2000. Ann Fam Med 3:60–3. doi: 10.1370/afm.214

8A. University of Ottawa Ethics certificate

File Number: H05-17-21 **Date (mm/dd/yyyy):** 06/05/2017

Université d'Ottawa
Bureau d'éthique et d'intégrité de la recherche

University of Ottawa
Office of Research Ethics and Integrity

Ethics Approval Notice

Health Sciences and Science REB

Principal Investigator / Supervisor / Co-investigator(s) / Student(s)

First Name	Last Name	Affiliation	Role
Ian	Colman	Medicine / Medicine	Supervisor
Kiyuri	Naicker	Medicine / Medicine	Student Researcher

File Number: H05-17-21

Type of Project: PhD Thesis – Secondary use of data

Title: Depression, Anxiety and Type 2 Diabetes: Associations with Diabetes Onset, Clinical Management and Mortality

Approval Date (mm/dd/yyyy)	Expiry Date (mm/dd/yyyy)	Approval Type
06/05/2017	06/04/2018	Approval

Special Conditions / Comments:
N/A

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8A. University of Ottawa Ethics certificate (continued)

File Number: H05-17-21 **Date (mm/dd/yyyy):** 06/05/2017

Université d'Ottawa
Bureau d'éthique et d'intégrité de la recherche

University of Ottawa
Office of Research Ethics and Integrity

This is to confirm that the University of Ottawa Research Ethics Board identified above, which operates in accordance with the Tri-Council Policy Statement (2010) and other applicable laws and regulations in Ontario, has examined and approved the ethics application for the above named research project. Ethics approval is valid for the period indicated above and subject to the conditions listed in the section entitled "Special Conditions / Comments".

During the course of the project, the protocol may not be modified without prior written approval from the REB except when necessary to remove participants from immediate endangerment or when the modification(s) pertain to only administrative or logistical components of the project (e.g., change of telephone number). Investigators must also promptly alert the REB of any changes which increase the risk to participant(s), any changes which considerably affect the conduct of the project, all unanticipated and harmful events that occur, and new information that may negatively affect the conduct of the project and safety of the participant(s). Modifications to the project, including consent and recruitment documentation, should be submitted to the Ethics Office for approval using the "Modification to research project" form available at: http://research.uottawa.ca/ethics/submissions-and-reviews.

Please submit an annual report to the Ethics Office four weeks before the above-referenced expiry date to request a renewal of this ethics approval. To close the file, a final report must be submitted. These documents can be found at: http://research.uottawa.ca/ethics/submissions-and-reviews.

If you have any questions, please do not hesitate to contact the Ethics Office at extension 5387 or by e-mail at: ethics@uOttawa.ca.

Signature:

Riana Marcotte
Protocol Officer for Ethics in Research
For Daniel Lagarec, Chair of the Health Sciences and Sciences REB

8B. Norwegian Research Ethics Board (REK) certificate

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK vest	Øyvind Straume	55978496	26.01.2015	2014/2160/REK vest
			Deres dato:	Deres referanse:
			09.12.2014	

Vår referanse må oppgis ved alle henvendelser

Børge Sivertsen
Avdeling for samfunn og psykisk helse

2014/2160 Mental helse og diabetes i HUNT

Forskningsansvarlig: Nasjonalt folkehelseinstitutt
Prosjektleder: Børge Sivertsen

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK vest) i møtet 08.01.2015. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10, jf. forskningsetikkloven § 4.

Prosjektomtale
Målet med prosjektet er å øke forståelsen av forholdet mellom diabetes og mentalvansker, og risiko for senere diabetes-relaterte komplikasjoner, herunder død. Hovedfokus er på lettere mentale lidelser, først og fremst symptomer på angst og depresjon. Tidligere studier har påvist en sammenheng mellom mentale vansker og diabetes, med fortsatt vet vi lite om hvordan slike symptomer påvirker forløpet av diabetes (både type 1 og 2). Et viktig punkt med dette prosjektet vil være å benytte nyere metodiske tilnærminger for å estimere mental lidelser, blant annet vil symptomer bli klassifisert ved hjelp av en bifaktoriell tilnærming, som har vist seg langt bedre enn vanlig to-faktor løsning (angst og depresjon) som inntil nå primært har blitt benyttet.

Vurdering

Søknad/protokoll
Dette er en registerstude basert på data fra HUNT. REK vest anser det brede samtykket i HUNT som dekkende, og bemerker at informasjonsopplegget i HUNT er meget bra. Prosjektet fremstår som ryddig, datalagringen trygg og komiteen har heller ingen merknader til studiens design.

Vedtak
REK vest godkjenner prosjektet i samsvar med forelagt søknad.

Sluttmelding og søknad om prosjektendring
Prosjektleder skal sende sluttmelding til REK vest på eget skjema senest 30.06.2019, jf. hfl. § 12. Prosjektleder skal sende søknad om prosjektendring til REK vest dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til REK vest. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK vest, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Besøksadresse:
Armauer Hansens Hus (AHH), Tverrfløy Nord, 2 etasje. Rom 281. Haukelandsveien 28

Telefon: 55975000
E-post: rek-vest@uib.no
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