Depression and anxiety symptoms in type 2 diabetes mellitus: a matter of time?

DOI:
10.4225/23/59a3cb711ef19

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Depression and Anxiety Symptoms in Type 2 Diabetes Mellitus: A Matter of Time?

Stephanie Rose Whitworth
Bachelor of Arts (Psychology), First Class Hons

This thesis is presented in total fulfillment of the requirements for the degree of Doctor of Philosophy and in partial fulfillment of the requirements for the degree of Master of Psychology (Clinical) of the University of Western Australia

School of Psychological Science

2017
I, Stephanie Rose Whitworth, certify that:

This thesis has been substantially accomplished during enrolment in the degree.

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The research involving human data reported in this thesis was assessed and approved by The University of Western Australia Human Research Ethics Committee Approval # RA/4/1/5798 and the South Metropolitan Area Health Service Ethics Committee Approval # 07/397.

Written patient consent has been received and archived for the research involving patient data reported in this thesis.

The work described in this thesis was funded by the National Health and Medical Research Council Project Grant 513781 and APP1042231.

This thesis contains published work and/or work prepared for publication, some of which has been co-authored.

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Abstract

Depression is the most widely studied psychological comorbidity for individuals with type 2 diabetes mellitus (T2DM) and confers significant burden to both the individual and healthcare system. Depression is implicated both in the risk of developing diabetes, and also as a risk factor for difficulties with diabetes self-management and glycaemic control. While research in this area is limited, evidence also suggests that anxiety frequently presents in this population and may affect disease outcomes. However, while T2DM is a chronic condition, the interrelationships between mood and diabetes management over time and implications for intervention remain to be clarified.

The overarching aim of this thesis was to delineate the longitudinal developmental pathways by which Major Depressive Disorder and Generalized Anxiety Disorder, separately and combined, impact on diabetes self-management, glycaemic control, and chronic health complications. This thesis adopted novel measures of lifetime depression and anxiety disorders to ascertain the association between long-standing psychological issues and diabetes-related outcomes. This thesis also aimed to clarify what qualifies as clinically meaningful psychological symptomatology in diabetes research. Thus, investigation of the associations between the severity of depression and anxiety symptoms over time, and implications for health-related outcomes, is a prominent theme of this thesis.

Study 1 (Chapter 2) explored the cross-sectional associations between a lifetime history of major depression and generalized anxiety disorder, and engagement in diabetes management and control. In a large cohort study of individuals with clinically
diagnosed T2DM, mediation models revealed a lifetime history of both disorders to be strong predictors of adverse outcome. Lifetime depression, by increasing the severity of current depression symptoms, emerged as an indirect predictor of current smoking, higher body mass index, less frequent blood glucose self-monitoring and worse glycaemic control. The most important finding was that, when co-occurring, a history of both depression and anxiety were indirectly related to the poorest disease management. This published study suggests that the chronicity and overlap of depression and anxiety symptoms may be of particular clinical relevance in diabetes.

Chapters 4 and 5 investigated the development and course of depression and anxiety symptoms in the same sample. Missingness emerged as a problem for interpretation of the longitudinal depression data. To address this, longitudinal missing data modeling was applied, and is presented in detail in Chapter 3. The identified model that best incorporated missingness in Chapter 3 was then adapted and used in Chapter 4.

Study 2 (Chapter 4) investigated the developmental course of depression symptoms over a 5-year period, and explored inter-relationships between depression symptoms and indices of diabetes management over time. Two sub-groups of individuals were identified who displayed a pattern of cycling and persistent depression symptoms, which cycled above and below cut-offs for clinically relevant depression but did not fully remit. Persistent-depression group members were more likely to be female, have higher body mass index, and a lifetime history of major depression. Persistent depression symptoms were not associated with the degree of change in BMI, blood-glucose self-monitoring, or HbA1c. This published study indicated that taking a broader
developmental perspective to the assessment of depression, might better capture the underlying persistence in these symptoms; something not typically screened for in diabetes care.

Study 3 (Chapter 5) extended these findings by examining the course of generalized anxiety symptoms over a 4-year period. Similarly, a sub-group of individuals were identified who experienced elevated, but gradually improving anxiety symptoms. Risk factors for membership to the elevated-anxiety group included lifetime anxiety and depression, more macrovascular complications, insulin use and hyperglycaemia. Supporting the results of Study 1, the most noteworthy finding was that there was a substantial overlap between depression and anxiety symptoms longitudinally. Two-thirds of those in the elevated anxiety group were also found to experience persistent depression symptoms, and this group displayed a more severe pattern of anxiety. This study highlighted the clinical importance of considering the development of, and interaction between, symptoms of both depression and anxiety in this population.

Chapter 6 concludes this thesis with a discussion of the key themes emerging from these studies, clinical implications, and future directions for psychosocial type 2 diabetes research. Taken together, the results indicate that screening for lifetime and current depression and anxiety symptoms in diabetes may facilitate more targeted psychological management and improved health outcomes.
Dedication

I dedicate this thesis to my Dad, the true storyteller. I took your advice and remembered to breathe. I know these words would make you proud.
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<td>BLDS</td>
<td>Brief Lifetime Depression Scale</td>
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<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>CBT</td>
<td>Cognitive Behaviour Therapy</td>
</tr>
<tr>
<td>CES-D</td>
<td>Centre for Epidemiologic Studies Depression Scale</td>
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<tr>
<td>DSM-IV</td>
<td>Diagnostic and Statistical Manual of Mental Disorders; 4th Edition</td>
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<tr>
<td>DSM-V</td>
<td>Diagnostic and Statistical Manual of Mental Disorders; 5th Edition</td>
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<tr>
<td>FDS2</td>
<td>Fremantle Diabetes Study-Phase II</td>
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<tr>
<td>GAD</td>
<td>Generalized Anxiety Disorder</td>
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<td>GAD-7</td>
<td>Generalized Anxiety Disorder 7-Item Scale</td>
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<td>GADS</td>
<td>Generalized Anxiety Disorder Scale</td>
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<td>GAD-LT</td>
<td>Generalized Anxiety Disorder – Lifetime Scale</td>
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<td>GGMM</td>
<td>General Growth Mixture Model</td>
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<td>GP</td>
<td>General Practitioner</td>
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<td>HADS</td>
<td>Hospital Anxiety and Depression Scale</td>
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<tr>
<td>HbA$_{1c}$</td>
<td>Glycated Haemoglobin</td>
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<tr>
<td>HPA-axis</td>
<td>Hypothalamic-Pituitary-Adrenal Axis</td>
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<tr>
<td>LCGA</td>
<td>Latent Class Growth Analysis</td>
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L-GAD  Lifetime Generalized Anxiety Disorder
L-MDD  Lifetime Major Depressive Disorder
MAR    Missing at Random
MBCT   Mindfulness Based Cognitive Therapy
MCAR   Missing Completely at Random
MDD    Major Depressive Disorder
NMAR   Not Missing at Random
PHQ-9  Patient Health Questionnaire-9 Item Version
PMM    Pattern Mixture Modeling
SCID-RV Structured Clinical Interview for DSM-IV-Research Version
SNS    Sympathetic Nervous System
SMBG   Self-Monitoring of Blood Glucose
SM     Selection Modeling
SPSS   Statistical Package for the Social Sciences
T2DM   Type 2 Diabetes Mellitus
Acknowledgements

“I get by with a little help from my friends”
- The Beatles

There are numerous people who have contributed to seeing this thesis through to fruition. I have come out the other end of the thesis tunnel thanks to you all.

First and foremost, I would like to extend an immense thank you to my research supervisors, who supported this fledgling researcher to get off the ground. To my primary supervisor, Romola Bucks. You have mentored, championed, and challenged me throughout this entire journey. I am the researcher I am today, because of your unwavering support. Thank you for always offering a rope when I fell down the rabbit hole. Here’s to many more cups of tea and big ideas.

To my co-supervisors, David Bruce and Sergio Starkstein. David, thank you for sharing your wealth of knowledge with me, and for your patience as I have navigated the world of Medicine. Your ongoing support, time, word cutting, and polite reception of an increasing number of emails, has been so appreciated. Sergio, thank you for sharing your wisdom in the field of Psychiatry, and for encouraging and supporting me throughout the process of my interview study. I have enjoyed our conversations to the backdrop of classical music. To Timothy Skinner, an honorary supervisor. Thank you for asking the challenging questions, and for your hours of time and direction. Your passion for health psychology is infectious.

This research was supported by an Australian Government Research Training Program (RTP) Scholarship, and a UWA University Postgraduate Award, Top-Up Scholarship and Completion Scholarship. I would like to thank the Graduate Research School and School of Psychological Science, for funding my travel to present and network at international conferences.
I would like to extend an enormous thank you to the Fremantle Diabetes Study team. Your years of dedicated work have enabled me to write this thesis. To Wendy Davis: thank you for your invaluable statistics advice, support of my data expeditions, and for your insight and conversation. To Timothy Davis, thank you for welcoming me into the fold, and for your helpful feedback along the way. It has been a privilege to learn from you both. Finally, to the participants of the FDS. This research was only possible because you generously donated your time, and your stories.

I would like to also extend thanks to the clinical supervisors who have guided my development as a therapist, and as a scientist. Special thanks to Neil McLean, Carmela Pestell, Susannah Flack, and Adele Summers, for inspiring my learning and encouraging me to lean into the discomfort. To Elli Roeder, thank you for seeing this through with me.

There are a number of friends I am truly grateful to know. To my psychology friend family; Olivia Carter, Jessica Tearne, Alice Gummery, and Alicia Wilson. To have met women as wonderful, insightful, validating and passionate as you, has made this degree infinitely worth it. To Michelle O’Keeffe, thank you for always reminding me there was an end in sight. To my postgraduate comrades: your company and support over the past 5 years has been invaluable. Special thanks to Kevin Mo and Jason Choi, and to my Sanders family, Jacqueline Stump, Steph Wade, Jessica Moncrieff-Boyd, Louise Delane, Alice Mason, and Shenooka Nanthakumar. A resounding thank you to my office mates, Sarah George, Shradha Kashyap and Briony Swire: every conversation, laugh and hot toddy, has kept me going.

To my girls. You know who you are. Thank you for providing me with food and wine, and multiple shoulders to lean on. I am so grateful to you all. Tegan Miller, thank you for the nights on the couch when they were all I could manage. Sheridan Coleman, thank you for being there to push me across the finish line.
Finally, to my family. I will forever be grateful for the unwavering support you all provide. Mum, I could not have done this without you. James, thank you for always having my back. Janny and Pop, thank you for teaching me to touch type - this thesis has been written much faster thanks to you. Finally, to my Dad. Thank you for the pride and confidence you had in my success. I wish you could be here to see this.
**Authorship Declaration: Co-Authored Publications**

This thesis contains work that has been published and prepared for publication.

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Details of the work:

Location in thesis: Chapter 5

Student contribution to work:
The student conceived and designed this study in collaboration with all co-supervisors. The student analyzed the data, interpreted findings, and prepared and revised the manuscript.

Student signature:

Date: 24th April 2017
On behalf of all co-authors, I, Romola S. Bucks certify that the student statements regarding their contributing to each of the works listed above are correct.

Coordinating Supervisor signature:

Date: 24th April 2017
Chapter 1: General Introduction

Depression and Anxiety Symptoms in Type 2 Diabetes Mellitus: A Matter of Time?

Over the past 30 years, the epidemic of obesity has increased exponentially worldwide. Alongside this epidemic, the prevalence of type 2 diabetes mellitus (T2DM) had dramatically increased and become the focus of significant study. While traditionally viewed as a condition of developed countries, T2DM has now become a global health crisis threatening the individual health and national economies of both developed and developing nations (F. B. Hu, 2011).

Adult T2DM: prevalence and healthcare implications

In 2015, the International Diabetes Federation estimated that approximately 8.8% of adults worldwide between the ages of 20 and 79, or 415 million people, were diagnosed with diabetes (Ogurtsova et al., 2017). By 2040, these estimates are expected to increase to 642 million people, or 1 in 10 adults (Ogurtsova et al., 2017). Economically, Australia has the highest spending on healthcare per person with diabetes (USD $7,652-$14,498), and the global health expenditures associated with T2DM are estimated to reach $USD 802 billion by 2040 (Ogurtsova et al., 2017). All reported statistics are conservative and may underestimate the true healthcare burden of diabetes, as between 28-80% of those with T2DM may remain undiagnosed (International Diabetes Federation Clinical Guidelines Task Force, 2012) and subsequently untreated.

T2DM is a chronic metabolic disorder associated with higher than normal blood glucose levels, termed hyperglycaemia, caused by deficits in insulin secretion and action (American Diabetes Association, 2006; DeFronzo et al., 2015). This disorder results in
dysregulation of carbohydrate, lipid and protein metabolism, and accounts for up to 90% of reported diabetes cases (American Diabetes Association, 2006). T2DM is traditionally diagnosed based on a combination of biochemical tests, including glycated haemoglobin (HbA1c) levels. HbA1c levels ≥ 6.5% (48 mmol/mol) indicate probable hyperglycaemia, and HbA1c levels can be used alone to diagnose T2DM, if two measurements are elevated in an asymptomatic individual. Diagnosis is frequently confirmed by an elevated random plasma glucose test (≥11.1 mmol/L) and fasting plasma glucose levels (≥7.0 mmol/L after 8 hours fasting) (American Diabetes Association, 2015; World Health Organization, 2011). Common symptoms of hyperglycaemia include thirst, polydipsia, polyuria/frequent urination, and fatigue (American Diabetes Association, 2006). While the cause of T2DM-related insulin-resistance is unknown, several biobehavioural risk factors have been implicated including higher body mass index (BMI), physical inactivity, poor diet, smoking, and a genetic predisposition (Chen, Magliano, & Zimmet, 2012; Grøntved & Hu, 2011; F. B. Hu, 2011).

In order to prevent the long-term health complications associated with T2DM, engagement in daily self-management is required by the individual to maintain optimal glycemic control. National and international recommendations suggest that individuals should aim to achieve an HbA1c target of ≤7% (53 mmol/mol), with this value ranging from 6-8% (42-64 mmol/mol) depending on the individual (Cheung et al., 2009; Inzucchi et al., 2012). A weight loss of 5-10%, in addition to increasing physical activity and moderating food intake, are also advised and have shown substantial benefit for
Depression and Anxiety in T2DM

improving HbA1c (Inzucchi et al., 2012). Thus, the burden of disease is high, as an individual is required regularly to self-monitor their blood glucose levels (SMBG; commonly through fingerpicking), adhere to diet and exercise recommendations, take oral glucose lowering medications as prescribed, and attend regular healthcare appointments (Bijl, Poelgeest-Eeltink, & Shortridge-Baggett, 1999). For some, but not all individuals, insulin treatment is also needed as their condition progresses (American Diabetes Association, 2006). Critically, when these behaviours are not undertaken, poorly controlled diabetes is associated with a host of adverse, long-term health outcomes. These include macrovascular complications such as cardiovascular disease and stroke; microvascular complications including retinopathy and peripheral neuropathy; foot ulcers, amputations, and mortality (Bruce, Davis, Starkstein, & Davis, 2005; de Groot, Anderson, Freedland, Clouse, & Lustman, 2001). The presence of diabetes complications confer even higher economic and individual costs (Simon et al., 2005).

Evidently, the successful management of diabetes is essential. Research over the past two decades has focused on ascertaining key predictors of poorer health behaviours and outcomes, and it is now widely recognized that mental health plays a crucial role (Young-Hyman et al., 2016). There are a broad spectrum of mental health problems present for individuals with diabetes, and an examination of all was beyond the scope of this thesis. Given their prevalence, overlap and detrimental impact, the symptoms of two primary psychological disorders were considered in depth: major depressive disorder (MDD) and generalized anxiety disorder (GAD).
Depression in T2DM

**Assessment of depression in T2DM.** MDD is most commonly identified as the experience of low mood (e.g. feeling sad) and/or a loss of interest or pleasure, persisting more days than not for at least two weeks. Using DSM-IV¹ criteria, the diagnosis of MDD is made if one of these symptoms are present, in addition to any of the following for a total of five: a significant increase or decrease in appetite or weight, insomnia or hypersomnia, psychomotor agitation or retardation, loss of energy, feelings of worthlessness or inappropriate guilt, difficulty with thinking or concentration, and suicidal ideation or intent (DSM-IV-TR; American Psychiatric Association, 2000). A significant impairment in social, occupational or other areas of functioning are required to warrant diagnosis. A diagnosis of minor depression, a milder form of depression, is made if between two-to-four symptoms are present, one of which is low mood or anhedonia.

While the gold-standard recommendation for identifying depression is through a clinical diagnostic interview such as the Structured Clinical Interview for DSM-IV Disorders (SCID-IV; First, Spitzer, Gibbon, & Williams, 2002), the utility of this time-consuming method is limited in primary care and research settings. A number of brief self-report instruments have been developed to screen for the presence of depression, including the Patient Health Questionnaire (Kroenke & Spitzer, 2002), Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983), and Center for Epidemiologic

¹ Note: there are no changes in the diagnosis of MDD between DSM-IV and DSM-5
Depression and Anxiety in T2DM

Studies – Depression Scale (CES-D; Radloff, 1977). Each scale typically provides: a total score that is the sum of all items, with higher scores indicating more severe depression symptoms (termed continuous depression severity); and a validated cut-point above which scores are termed clinically meaningful and suggest probable depression (elevated depressive symptoms) (Kroenke & Spitzer, 2002). The PHQ-9 is also structured to suggest the presence of a MDD diagnosis (depression), by mapping symptoms against diagnostic criteria.

Prevalence and impact of depression in T2DM. As the most studied psychological comorbidity in T2DM, it is widely recognized that depression confers additional burden for both the individual and the healthcare system. Rates of depression are high, with clinically significant depression estimated to be twice as prevalent in people with diabetes as in the general population (Egede, Zheng, & Simpson, 2002). More recent meta-analytic evidence suggests these estimates may be closer to a 15%-23% increased risk of depression (Hasan, Clavarino, Mamun, Doi, & Kairuz, 2013; Mezuk, Eaton, Albrecht, & Golden, 2008), with up to 70% of this population experiencing some depressive symptoms (Gonzalez, Safren, et al., 2008).

At an individual level, the presence of depression or elevated depressive symptoms is associated with less engagement in all self-care behaviours, treatment non-adherence, and risk of all micro-and-macrovascular complications (Ciechanowski, Katon, Russo, & Hirsch, 2003; de Groot et al., 2001; Gonzalez et al., 2007; Gonzalez, Peyrot, et al., 2008). Further, despite disagreement regarding the strength of this association, a breadth of literature has demonstrated a significant but small-to-medium
Depression and Anxiety in T2DM

Effect of depression on hyperglycaemia (Fisher et al., 2008; Gois, Dias, Raposo, do Carmo, & Barbosa, 2012; Lustman, Anderson, et al., 2000). Unsurprisingly, depression in diabetes therefore incurs significantly higher healthcare costs and resource use (Egede et al., 2002; Simon et al., 2005), with costs highest for those with more severe depressive symptoms (Ciechanowski, Katon, & Russo, 2000). Of greatest clinical concern, the comorbidity of depression in diabetes substantially increases the risk of mortality (Bruce et al., 2005; Katon et al., 2005).

Anxiety in T2DM

Assessment of anxiety in diabetes. A number of anxiety disorders present frequently in individuals with a chronic medical illness, including panic disorder, post-traumatic stress disorder, social phobia, and generalized anxiety disorder. All anxiety disorders share key features of anxious cognitions, physiological symptoms, and behavioural difficulties (Smith et al., 2013). Of these disorders, generalized anxiety disorder (GAD) is the most common to present in primary care (Tylee & Walters, 2006). GAD is manifested by persistent worry and/or anxiety about a number of areas of life, which is difficult to control. In addition to these cardinal symptoms, a diagnosis of GAD is made if an individual also experiences three or more of the following symptoms, more days than not for at least six months: restlessness/feeling on edge, fatigue, difficulty concentrating, irritability, muscle tension, and sleep disturbance (DSM-IV-TR; American Psychiatric Association, 2000). A diagnosis is confirmed if these symptoms have a significant impact on an individuals’ daily functioning.
Similar to MDD, a number of self-report measures screen for anxiety, including providing a total score of anxiety severity (termed continuous anxiety severity), a clinical cut-point above which scores indicate likely detection of GAD (elevated anxiety symptoms), and a probable diagnosis of GAD (anxiety). Validated instruments include the Generalized Anxiety Disorder-7 (GAD-7; Spitzer, Kroenke, Williams, & Lowe, 2006), the Generalized Anxiety Disorder Scale (GADS; Starkstein et al., 2014), and the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983).

**Prevalence and impact of anxiety in T2DM.** Overall, substantively less is known about anxiety than depression in diabetes. This is of concern as a recent meta-analysis found that, across 12 studies including 12,626 individuals, diabetes led to a 20% increase in the prevalence of anxiety disorders and 48% increase in anxiety symptoms (Smith et al., 2013). Prevalence estimates for sub-threshold anxiety (anxiety symptoms which fall below a clinical cut-off), or for elevated anxiety symptoms, are routinely higher than those for GAD diagnosis (Grigsby, Anderson, Freedland, Clouse, & Lustman, 2002; Smith et al., 2013).

Studies of the association between anxiety and diabetes management/control are variable. First, elevated anxiety has been shown to be associated with increased insulin use, uncertainty about glycemic control, more diabetes complications, and more painful diabetic peripheral neuropathy (Collins, Corcoran, & Perry, 2009; Gore et al., 2005), but may not impact on adherence to medical recommendations (DiMatteo, Lepper, & Croghan, 2000). Second, there is a lack of agreement in the literature regarding the impact of anxiety on glycemic control. Some studies have found a significant
relationship (Anderson et al., 2002; Balhara & Sagar, 2011), while others have not (Fisher et al., 2008; Gois et al., 2012). Given the limited investigation of anxiety in diabetes, the broader burden of GAD on the healthcare system is also unclear. However, general population studies have demonstrated that GAD is associated with higher primary and specialist care use, higher medical costs (Bereza, Machado, & Einarson, 2009) and greater disability (Porensky et al., 2009).

Taken together, there is strong evidence that depression is a detrimental comorbidity for individuals with diabetes, and that anxiety may affect outcomes to a lesser degree. However, MDD and GAD are also highly comorbid disorders in the general population (Merikangas et al., 2003), resulting in even higher healthcare costs (Boulanger, Zhao, Bao, & Russell, 2009), more chronic psychopathology, and lower remission rates in both disorders over time (Merikangas et al., 2003; Penninx et al., 2011; Schoevers, Deeg, van Tilburg, & Beekman, 2005). This comorbidity may be more prevalent in diabetes than the general population (Deschênes, Burns, & Schmitz, 2015), affecting up to 17.2% of individuals (Collins et al., 2009). One study identified a small group of individuals who experienced a high overlap in depression and anxiety symptoms, which the authors termed major anxious depression (Starkstein et al., 2014). These individuals had poorer glycemic control and higher rates of insulin use than those with subclinical or no mood symptoms. While it can be posited that diabetes management and control may be even worse for these individuals, a paucity of research exists in this area. To further complicate the picture, assessment of the individual impact of either MDD or GAD often does not control for the other, confounding the
relationships observed (Collins et al., 2009; Fisher et al., 2008). Thus, a key aim of Chapter 2 of this thesis is to clarify the separable and combined effect of MDD and GAD in T2DM, in order to facilitate more appropriate and targeted intervention.

In addition to the impact of depression and anxiety in this population, recent research has focused on another concomitant psychological construct in T2DM, termed diabetes-specific emotional distress (diabetes distress; Fisher et al., 2010). Diabetes distress refers to the worries, concerns and fears of the individual living with diabetes, and reflects a broader affective experience to that captured by depression and anxiety symptom measures (Fisher, Gonzalez, & Polonsky, 2014). Diabetes distress has been found to be a significant predictor of diabetes self-care and glycaemic control (Fisher et al., 2010; Gonzalez, Safren, et al., 2008) and to be associated with symptoms of depression (Ehrmann, Kulzer, Haak, & Hermanns, 2015). There exists debate in the field regarding whether the prevalence of depression, in particular, and the association between depression and health-related outcomes, may in part be explained by elevated levels of diabetes distress (Fisher et al., 2010; Snoek, Bremmer, & Hermanns, 2015). However, it was beyond the scope of this thesis to include a thorough assessment of diabetes distress, and the well-established psychiatric constructs of depression and anxiety will be the primary focus. A more detailed discussion of this debate is provided in Chapter 6.

**Depression, anxiety and diabetes: developmental considerations**

International recommendations now emphasize the need for improved screening, monitoring, and treatment of psychological distress in diabetes in order to improve
biopsychosocial outcomes (American Diabetes Association, 2017; International Diabetes Federation Clinical Guidelines Task Force, 2012). While psychological treatments, including Cognitive Behavioural Therapy (CBT), have demonstrated efficacy in improving depression in diabetes (Lustman, Griffith, Freedland, Kissel, & Clouse, 1998), and may translate to better self-care and glycemic control when combined with adherence training (Safren et al., 2014), detection rates of mood disorders are low (Petrak, Baumeister, Skinner, Brown, & Holt, 2015). Moreover, many of these recommendations are based on findings from cross-sectional studies, yet T2DM and mood disorders are dynamic processes that change over the life course (DeFronzo et al., 2015; Merikangas et al., 2003). A number of developmental factors that may contribute to improvements in screening and treatment processes warrant consideration. These include: 1) the bidirectional association between mood and T2DM; 2) the longitudinal course of depression and anxiety in T2DM; and 3) the complex interrelationships between changes in mood and T2DM management over time. Each topic is outlined, in detail, below.

**Depression, anxiety and diabetes: a bidirectional relationship**

The aforementioned relationships between depression, anxiety and T2DM are now known to be bidirectional. First, depression and to a lesser extent anxiety, can increase the risk of developing diabetes (Edwards & Mezuk, 2012; Engum, 2007; Knol et al., 2006; Mezuk et al., 2008). Depression may contribute through its association with poorer self-care, smoking, obesity, sedentary behaviour (Katon, 2003), and difficulty collaborating with healthcare professionals (Ciechanowski, Katon, Russo, & Walker,
Depression and Anxiety in T2DM

2001). Through shared inflammatory pathways, depression and anxiety can also lead to increased production of pro-inflammatory cytokines, hypothalamic-pituitary axis (HPA) and sympathetic nervous system (SNS) activation, and biological changes due to long-term antidepressant use: all risk factors for maladaptive immune and endocrine changes (Barnard, Peveler, & Holt, 2013; Black, 2003; Kiecolt-Glaser & Glaser, 2002). Second, T2DM can lead to the development of depression and anxiety symptoms due to the psychosocial burden of managing a chronic condition, including long-term insulin use, fear of hypoglycemia, and the development or worsening in health complications (Collins et al., 2009; Culpepper, 2009; Trento et al., 2015). Underlying vascular, inflammatory and neurohormonal changes associated with diabetes may also play a role in the risk of depression and anxiety (Bruce et al., 2006; Culpepper, 2009). Finally, common factors associated with depression and diabetes, including obesity, inactivity, inflammation, and low socio-economic status, may cumulatively contribute to the risk of both conditions (Everson, Maty, Lynch, & Kaplan, 2002; Tabák, Akbaraly, Batty, & Kivimäki, 2014).

Despite this substantial body of research, the impact of the directionality of these associations on long-term mood and disease management has received little attention. One method of delineating this is to examine the effect of lifetime mood problems on later psychological and health-related outcomes. Evidence suggests that experiencing a past or lifetime episode of depression (lifetime major depressive disorder; L-MDD) is associated with less engagement in self-management behaviour, non-attendance at healthcare appointments and risk of treatment dropout, and with a higher incidence and
recurrence of depressive symptoms, minor and major depression (Bruce, Davis, Hunter, et al., 2016; Bruce, Davis, Cetrullo, Starkstein, & Davis, 2013; Marcus, Wing, Guare, Blair, & Jawad, 1992; Naranjo, Fisher, Areán, Hessler, & Mullan, 2011; Nefs, Pouwer, Denollet, & Pop, 2012; Wagner, Tennen, & Osborn, 2010). However, most available studies are limited in generalizability due to the recruitment of women without current MDD only (Wagner et al., 2010), overweight individuals self-selecting to a weight-loss group (Marcus et al., 1992), or by excluding individuals with MDD at baseline (Naranjo et al., 2011). Of clinical relevance, the separable impact of lifetime generalized anxiety disorder (L-GAD) on later outcomes, and the likely exacerbating effect of comorbid L-MDD+L-GAD on adverse psychological and physical health, has not been investigated. The primary aim of Chapter 2 (Study 1) of this thesis is to elucidate the impact of L-MDD and L-GAD in a representative sample of individuals with T2DM and address implications for intervention.

**The course of depression and anxiety in T2DM**

Supporting the use of a life-course developmental perspective, a large number of studies have demonstrated that MDD is recurrent and chronic in diabetes. A depression diagnosis has been shown to be persistent for up to one third of patients (Nefs et al., 2012; Peyrot & Rubin, 1999), with high rates of recurrence in pre-post follow-up periods ranging from 6 months to 5 years (Katon et al., 2009; Lustman, Griffith, Freedland, & Clouse, 1997; Peyrot & Rubin, 1999). Rates of symptomatic persistence are even higher when considering the experience of elevated depressive symptoms (Fisher et al., 2008). More recently, a study by Schmitz and colleagues (2013) found separate classes of
individuals who changed differentially in their depression diagnoses over time. While the majority of their sample were not depressed over 3 years (67%), a sub-set showed a pattern of increasing major depression (6%), improved depression (7%), or increasing prevalence of major and minor depression (20%; Schmitz et al., 2013). The course of continuous depression severity, rather than depression diagnosis, over time remains to be examined.

Unsurprisingly, there is a dearth of research regarding the course of GAD in T2DM. General population studies lack agreement based on the time frame and age group adopted, with some studies suggesting that GAD is persistent with a pattern of relapse and remission over time (Keller, 2002; Schoevers et al., 2005), while others have found GAD to decline steadily over 14 years in middle adulthood (Ramsawh, Raffa, Edelen, Rende, & Keller, 2009), or to show the greatest initial decrease within 2 years of diagnosis (Yonkers, Bruce, Dyck, & Keller, 2003). Only one study has investigated the course of GAD over more than 2 time points in diabetes, finding an episodic pattern whereby 27% of those who met criteria at baseline continued to do so at the second wave, and only 19% did so at the third (Fisher et al., 2008).

**Depression, anxiety and diabetes management over time**

Few studies have examined the relationship between the course of depression/anxiety, and change in diabetes management and outcomes. Available evidence suggests that diabetes-related risk factors for persistence in elevated depression symptoms include insulin use, higher BMI, and diabetes-specific distress (Skinner et al., 2010; Trento et al., 2015). Poorer glycemic control has also been shown to predict
persistent depression in some (Fisher et al., 2008), but not other (Fisher et al., 2010; Skinner et al., 2010) studies. Long-standing diabetes complications, or the development of new complications, may also produce worsening in depression over time (Fisher et al., 2008; Katon et al., 2009), in turn increasing cardiovascular risk (Windle & Windle, 2013) and poorer self-care (Gonzalez, Safren, et al., 2008). For anxiety, similar patterns emerge, with more diabetes complications, higher BMI, and smoking linked to elevated anxiety over time (Fisher et al., 2008; Trento et al., 2015), while HbA1c was not (Fisher et al., 2008).

**Limitations of current developmental perspectives**

Mood and diabetes exhibit bidirectional associations that appear to influence the progression of each over time. These associations may have significant implications for the timing and nature of interventions aiming to improve both psychological and diabetes outcomes. However, the available literature has been limited by a number of methodological issues that hinder our understanding of these relationships, including: 1) issues of study design; 2) problems with the assessment of depression and anxiety; and 3) suboptimal statistical methods of studying change. These issues are each discussed, in turn, below.

**Study design.** Briefly, all examined studies have been primarily incidence or prevalence designs with data assessed at just two time points (Gonzalez, Safren, et al., 2008; Trento et al., 2015), biased by Type 1 diabetes samples (Katon et al., 2009), or have examined only one direction in these interrelationships (Fisher et al., 2008; Gonzalez, Safren, et al., 2008; Skinner et al., 2010; Trento et al., 2015). For example, the
majority of studies have investigated diabetes-related factors as a predictor of persistence or change in mood symptoms (Fisher et al., 2008; Katon et al., 2009), but not the reverse. Taken together, this has not allowed for a comprehensive examination of the longer-term, naturalistic course of depression and anxiety in diabetes, or for delineating the developmental associations between changes in mood and changes in diabetes management.

**Assessment of MDD and GAD.** Existing longitudinal studies have conceptualized mood based on clinical diagnosis or as scoring above a clinical cut-point on self-reported mood scales (Fisher et al., 2008; Schmitz et al., 2013). However, the experience of subthreshold depression, with symptoms that may be less severe than these cut-points but still clinically meaningful, has been linked to greater psychosocial dysfunction, impaired health-related quality of life, and risk of later depressive episodes (Kennedy, Abbott, & Paykel, 2004; Sadek & Bona, 2000; Schmitz et al., 2014; Wells, Burnam, Rogers, Hays, & Camp, 1992). Subthreshold depression and anxiety symptoms may often remain elevated and unremitting, and fluctuate in severity over time (Keller, 2002; Merikangas et al., 2003). Researchers have thus argued for consideration of mood as a continuous construct better to capture this heterogeneity (Fisher, Gonzalez, & Polonsky, 2014; Gonzalez, Fisher, & Polonsky, 2011), but the use of continuous mood scores is infrequent, especially in longitudinal studies.

The strength of the associations between mood and diabetes management also differ based on the assessment method adopted. Gonzalez and colleagues (Gonzalez et al., 2007) found continuous depression severity to be a better predictor than a diagnosis
of MDD of non-adherence to diet and exercise recommendations, while MDD diagnosis more strongly predicted less frequent SMBG. Another study found elevated depressive symptoms, albeit above a clinical cut-point, to be more closely related to HbA1c than MDD diagnosis (Fisher et al., 2008). Differential associations based on the method of anxiety assessment are unclear.

Furthermore, the course of continuous depression and anxiety severity over time, and associations with T2DM, have not been examined. This may provide a more concise and detailed picture of the gradual symptomatic change in these disorders, and improve identification of those with subthreshold but potentially meaningful symptoms. Exploration of the overlap in symptoms of depression and anxiety over time may also be revealing. These are the primary aims of Chapters 4 and 5 of this thesis.

**Statistical methods of studying change.** The previously mentioned traditional approaches of studying change aim to investigate relationships among variables. In doing so, they provide an estimate of change for the entire sample (B. O. Muthén & Muthén, 2000). For mood disorders that are heterogeneous in the general population, this “one size fits all” approach is unlikely to accurately represent symptomatic change over time for the individual (Nagin & Odgers, 2010). Instead, latent class growth modeling (LCGA) and latent growth mixture modeling (LGMM) approaches have risen in popularity as a method to address this issue. These approaches aim to determine both the individual’s trajectory of change (interindividual change), and whether there exist broader patterns of similarities in change for groups of individuals (intraindividual change; (Jung & Wickrama, 2008). Predictors and outcomes of identified trajectories
can also be examined (B. O. Muthén & Muthén, 2000). These approaches have been used to study trajectories of alcohol dependence (B. O. Muthén & Muthén, 2000), depression and anxiety symptoms following spinal cord injury (Bonanno, Kennedy, Galatzer-Levy, Lude, & Elfström, 2012) and in musculoskeletal pain (Rzewuska, Mallen, Strauss, Belcher, & Peat, 2015), and one study has investigated trajectories of change in depression diagnoses over time in diabetes (Schmitz et al., 2013).

Existing methodologies may also lead to biased results due to how missing data are handled. Traditional, longitudinal analyses exclude individuals with missing data at any one time point (Enders & Bandalos, 2001). These methods likely bias estimates and do not allow inclusion of those who may intermittently drop out and then return throughout a study (Enders, 2010). LCGA and LGMM methods allow for missingness to be modeled as part of each analysis, maximizing the number of participants included and providing a more accurate change estimate. Chapter 3 provides a comprehensive description of how missing values analysis was conducted for the longitudinal LCGA analyses reported in this thesis.

**Summary and contents of chapters**

T2DM is a highly prevalent and chronic condition that causes significant cost to the individual and economy. A large body of research has indicated that depression, and to a lesser extent anxiety, increase the risk of poorer psychosocial and health-related outcomes in this population. However, the developmental pathways by which depression and anxiety symptoms may, either separately or combined, develop and affect diabetes-related outcomes remain unclear.
The primary aim of this thesis was to investigate and clarify the strength of these associations and implications for intervention in a representative community sample of individuals with T2DM. In particular, this thesis examined the complex interrelationships between lifetime MDD and GAD, current depression and anxiety symptoms, and diabetes management by adopting a longitudinal, trajectory perspective.

To do this, Study 1 (Chapter 2) first involved a cross-sectional examination to delineate the separate and combined impact of lifetime MDD and lifetime GAD on continuous depression and anxiety symptoms and health outcomes. It was hypothesized that individuals with a lifetime history of MDD, GAD, or both, would experience more severe current mood symptoms and have worse health-related outcomes than those with no history of either disorder. This study was published in the journal *Diabetes Research and Clinical Practice* (2016); 122; 190-197.

Prior to determining trajectories of continuous depression and anxiety symptoms, missing values analyses were performed in order to examine any bias in estimates that may be due to missing data. Chapter 3 presents a detailed analysis of missingness in longitudinal data, and provides the rationale for analyses performed in Chapter 4.

Importantly, the developmental trajectories of depression and anxiety diagnoses appear to differ both in the general population and in T2DM (Fisher et al., 2008; Merikangas et al., 2003), and may affect diabetes outcomes differentially. Thus, before examining the impact of the overlap in these disorders over time, it was first necessary to understand the naturalistic course of depression and anxiety symptom trajectories separately. Chapter 4 (Study 2) used the findings from the missing values analysis in
Chapter 3 in a latent class growth model, to examine the course of depression symptoms over 5 years in T2DM. Associations of these trajectories with corresponding longitudinal changes in HbA₁c, BMI, and SMBG, were explored. It was hypothesized that separable groups of individuals would be identified who experienced a similar pattern of depression symptom severity over time, and that those experiencing ongoing threshold or subthreshold depression would be at greater risk of adverse long-term health outcomes. This chapter has been accepted for publication in *Diabetic Medicine* as of April 2017.

The final, investigative chapter (Chapter 5, Study 3) developed the findings from Chapter 4 and used latent growth mixture modeling to determine trajectories of anxiety symptoms over 4 years in the same sample. HbA₁c, BMI, SMBG, and health complications were investigated as predictors and outcomes of these trajectories. The proportion of overlap between depression trajectories determined from Chapter 4 (Study 2), and the identified anxiety symptom trajectories, was then examined. As in Chapter 4, it was hypothesized that separate groups of individuals would be identified who experienced similar trajectories of anxiety symptoms over time, and that individuals with overlapping anxiety and depression trajectories would display worse psychological and health-related outcomes. This Chapter has been prepared as a manuscript for submission to *Diabetes Care*.

The final chapter of this thesis, Chapter 6, provides a comprehensive discussion of the findings, strengths, limitations and clinical implications.
Each Chapter has been formatted according to the journal in which the Study was published, or for which it was prepared for publication. Thus, specific formatting may differ between Chapters.
Chapter 2: Lifetime Depression and Anxiety Increase Prevalent Psychological Symptoms and Worsen Glycemic Control in Type 2 Diabetes

This chapter was published in the journal Diabetes Research and Clinical Practice: Whitworth, S.R., Bruce, D.G., Starkstein, S.E., Davis, W.A., Davis, T.M.E., Bucks, R.S. (2016). Lifetime depression and anxiety increase prevalent psychological symptoms and worsen glycemic control in type 2 diabetes: the Fremantle Diabetes Study Phase II. Diabetes Research and Clinical Practice; 122; 190-7. It is presented below, as published, but formatted for consistency with the rest of the thesis.

Preface

Depression and anxiety are highly comorbid in type 2 diabetes, yet the interplay between a lifetime history of major depression, generalized anxiety disorder, and diabetes management and glycaemic control remain unclear. Importantly, the separate and combined influence of a history of GAD in this population has not previously been investigated. Chapter 2 presents a cross-sectional examination, using indirect mediation models, of the risk associated with both historical and current MDD and GAD in diabetes.
Abstract

**Aims:** To determine the contribution of lifetime major depressive disorder (L-MDD) and lifetime generalized anxiety disorder (L-GAD) to current psychological symptom severity, health behaviour and glycaemic control in type 2 diabetes.

**Methods:** 1,285 community-dwelling people with type 2 diabetes (Fremantle Diabetes Study Phase-II; FDS2) completed the PHQ-9 and Brief Life-time Depression Scale (BLDS) to assess current and past MDD. The Generalized Anxiety Disorder Scale (GADS) and the Generalized Anxiety Disorder Scale-Lifetime (GAD-LT), designed for FDS2, assessed current and past anxiety. Data were analysed using analysis of covariance and multiple mediation models, controlling for age, gender, marital status, and diabetes duration.

**Results:** L-MDD and L-GAD were independently associated with more severe current depression (both $P<0.001$) and anxiety (both $P<0.001$) symptoms. Mediation models revealed that, through increasing the severity of current depressive symptoms, L-MDD was associated with higher HbA$_1$c and body mass index (BMI), greater likelihood of current smoking, and reduced self-monitoring of blood glucose (SMBG) (indirect regression path ab, all $P<0.001$). In combination, L-MDD+L-GAD additionally elevated the risk of higher HbA$_1$c and worse diabetes management, by increasing the severity of current depressive symptoms (indirect regression path ab, all $P<0.001$).

**Conclusions:** Lifetime depression and anxiety increase risk of more severe psychological symptoms, hyperglycaemia, and difficulties with health behaviour in type
2 diabetes. Early screening for these disorders at diabetes diagnosis may be warranted to maximize long-term health outcomes.
Introduction

Clinical depression and anxiety symptoms are highly prevalent in people with type 2 diabetes (de Groot et al., 2001), and are associated with suboptimal self-management behaviour, poor glycaemic control, obesity (Katon et al., 2004), chronic complications and mortality (de Groot et al., 2001; Gonzalez, Peyrot, et al., 2008). This relationship is known to be bidirectional, whereby depression and anxiety can increase the risk of diabetes onset, or develop as a consequence of diabetes disease burden and management (Bruce et al., 2013; Renn, Feliciano, & Segal, 2011; Trento et al., 2014, 2015). For individuals already diagnosed with diabetes, better prediction of those at elevated risk of developing or worsening depression and anxiety is required to enable earlier identification and treatment. A history of depression (lifetime major depressive disorder; L-MDD) has been associated with an increased risk of current major depression diagnosis, reduced rates of SMBG (Wagner et al., 2010) and risk of diabetes complications (Bruce et al., 2013). Furthermore, one study of obese people with diabetes found L-MDD to be associated with greater severity of current depressive symptoms and increased treatment attrition (Marcus et al., 1992). Screening for L-MDD may therefore provide a valuable opportunity for identifying those at risk of experiencing more severe psychological symptoms and worse health outcomes, particularly if these individuals do not present with current symptoms.

The impact of lifetime anxiety has not been investigated previously in this population. Anxiety affects up to 40% of people with diabetes, with 14% experiencing current generalized anxiety disorder (GAD; Grigsby et al., 2002). Moreover, depression
and anxiety symptoms occur together in up to 17.2% of patients (Collins et al., 2009), and this comorbidity is associated with greater resistance to psychological treatment (Fisher et al., 2008), reduced rates of remission in both disorders over time (Schoevers et al., 2005) and significantly more diabetes complications (Collins et al., 2009). In a recent, large, community-based study, we identified a group of individuals experiencing severe depression and anxiety symptoms who exhibited higher HbA1c levels and a greater requirement for insulin (Starkstein et al., 2014). Given that anxiety symptoms are seldom assessed in studies of diabetes, investigation of the impact of lifetime anxiety, and of comorbid lifetime depression and anxiety, on diabetes and its sequelae is needed.

The present prospective cohort study investigated the impact of lifetime major depressive disorder (L-MDD) and lifetime generalized anxiety disorder (L-GAD), on current depression and anxiety symptom severity and diabetes control in 1,285 individuals with type 2 diabetes. The aims of the present study were to determine whether (i) L-MDD and/or L-GAD are associated with more severe depression and anxiety symptoms in type 2 diabetes, (ii) L-MDD and/or L-GAD predict risk of worse health behaviour and diabetes control, and (iii) comorbid L-MDD+L-GAD increase risk of more severe mood symptoms and inappropriate diabetes control, than experiencing either disorder alone. It was hypothesised that the effect of L-MDD and/or L-GAD on health behaviour and diabetes control may occur indirectly by increasing the severity of current depression and anxiety symptoms which, in turn, impact on diabetes health behaviours.
Materials and Methods

Study participants

The Fremantle Diabetes Study Phase II (FDS2) is a longitudinal study of known diabetes, conducted in a postcode-defined, geographical area surrounding the city of Fremantle in the state of Western Australia (Davis, Bruce, & Davis, 2013). Recruitment, study procedures, classification of diabetes type and sample characteristics are reported elsewhere (Davis et al., 2013). Briefly, residents (n=1732) identified as having diabetes were recruited to FDS2 between 2008 and 2011. Patients were excluded if they did not have clinically diagnosed type 2 diabetes, or were under 18 years, leaving a final sample of n = 1549. FDS2 was approved by the Human Research Ethics Committee of the South Metropolitan Area Health Service, and participants gave written, informed consent.

The FDS2 has a number of strengths. This study is based on a large, well-characterized community-based cohort. The FDS2 covers a region which captures varied socio-economic backgrounds and multi-ethnic communities, including migrants and Indigenous persons (Davis et al., 2015, 2013). This study also involved a comprehensive clinical assessment and diagnosis of T2DM using a clinical algorithm, which was validated using the Western Australian Data Linkage System (Davis et al., 2013). Further the FDS2 both utilized, and developed, validated instruments for measuring depression and anxiety. Limitations of the FDS include recognized bias associated with
observational studies, such as recruitment and survivor bias (Davis et al., 2013), and the use of self-reported measures of mood rather than clinical diagnostic interviews².

**Study procedures**

At study entry, participants completed a comprehensive interview, questionnaire, and clinical examination. Clinical examination included standard fasting biochemical tests such as fasting serum glucose and HbA₁c, and body mass index (BMI) measurement (kg/m²). The questionnaire included demographic information, details of diabetes and other illnesses, diabetes duration, current blood glucose-lowering treatment (diet/exercise, oral hypoglycemic agents with or without insulin) and antidepressant use. Behavioural factors associated with diabetes management, including smoking status, alcohol consumption (number of standard alcohol drinks consumed per day), and SMBG, were self-reported at interview.

**Assessment of depression and anxiety**

The Patient Health Questionnaire-9 item version (PHQ-9; Kroenke & Spitzer, 2002) was used to assess current depressive symptoms and severity, and the likely presence of major depressive disorder. A PHQ-9 diagnosis of probable major depression has good agreement with structured interview diagnoses (Spitzer, Kroenke, & Williams, 1999), and is validated for use in diabetes (van Steenbergen-Weijenburg et al., 2010). Each symptom is scored positively if endorsed as “more than half the days” or “nearly every day”, with probable major depression defined as experiencing 5 or more positive

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² This paragraph was added to this Chapter on examiner request, and was not included in the published manuscript.
depressive symptoms over the past two weeks, with a least one being either loss of interest or feeling depressed (Spitzer et al., 1999). Total scores range from 0-27, with higher scores indicative of more severe depressive symptoms. Symptom severity was categorized as no symptoms (0-4), mild (5-9), moderate (10-14), moderately severe (15-19) and severe depression (20+; Spitzer, Kroenke, & Williams, 1999).

The Brief Life-Time Depression Scale (BLDS; Bruce et al., 2013) was used to assess the lifetime prevalence of major depressive disorder. This measure was modeled on the PHQ-9, and includes similar items, general format and language, but asks participants to rate whether they have ever experienced any of the nine symptoms of depression listed in the DSM-IV for a period of 2 weeks or more. Information on functional impairment, when the symptoms were first experienced (age and year), duration of episode, and any treatment sought was also collected. Lifetime diagnosis of major depression was classified using DSM-IV criteria as outlined above. Further detail on the development and use of the BLDS is reported elsewhere (Bruce, Davis, Hunter, et al., 2016; Bruce et al., 2013), and this measure has been validated against the Structured Clinical Interview for DSM-IV (SCID) Affective Disorders Module in type 2 diabetes with sensitivity = 92.5% and specificity = 100% (Bruce et al., 2013).

Current anxiety symptoms and severity were assessed using the Generalized Anxiety Disorder Scale (GADS; Starkstein et al., 2014), developed in FDS2 to map directly onto the nine DSM-IV criteria for GAD. Based on PHQ-9 formatting, GADS items were rated as “not at all present”, “present several days”, “present more than half of the days”, and “present nearly every day”, with an item scored positively if endorsed
as “more than half the days” or “nearly every day”. To be comparable to the DSM-IV criteria for GAD, the time criterion was the past 6 months. Probable GAD was classified if individuals scored positively for excessive worry and difficulty controlling their worries, in addition to 3 or more positive anxiety symptoms. Information on functional impairment, as well as possible drug or medical illness causes for anxiety, was collected. This measure has high diagnostic concordance with the Structured Clinical Interview for DSM-IV-Research Version (SCID-RV)-Anxiety disorders Module (kappa=0.88; Starkstein et al., 2014), and high internal consistency (Cronbach’s α =0.89). Total scores range from 0-24, with higher scores indicative of more severe anxiety symptoms.

For the study of lifetime anxiety, a specific questionnaire (the Generalized Anxiety Disorder – Lifetime Scale (GAD-LT) was devised by one of the authors (SES) with experience in developing psychiatric instruments to rate the severity of anxiety. This measure was developed for FDS2 to map onto the GADS, and the time criterion was set to one month to reflect DSM-IV lifetime criteria as assessed in the SCID-RV. Participants are asked to rate whether they have experienced a period in their lives, lasting for more than one month, during which they worried excessively or were anxious about several things, or found it difficult to control their worries. If either symptom is endorsed, the participant is asked to indicate if they experienced additional symptoms during that period, namely feeling restless, tense, tired, difficulty concentrating, felt irritable, or had difficulty sleeping. Data on functional impairment, when the symptoms were first experienced (year), duration of the episode, and treatment sought were collected. Lifetime diagnosis of GAD was classified using DSM-IV criteria as outlined
above. This measure was validated in a convenience sample of 24 FDS2 participants against the SCID-RV-Anxiety Disorders Module. Kappa statistics showed high diagnostic concordance (kappa = 0.91). Eight of the 24 patients received a diagnosis of lifetime GAD based on the SCID compared to 9 on the GAD-LT. Test-retest reliability was assessed in another 24 participants who completed the GAD-LT twice, 9±6 days apart. The intra-class correlation (ICC for total score = 0.96) was excellent.

For individuals who met L-MDD and L-GAD criteria, the time period rated, episode duration, and number of past episodes was compared with the PHQ-9 and GADS to ensure no overlap between current and past diagnoses. Individuals were classified as having either pure MDD or pure GAD only, by excluding those with the other disorder.

**Statistical analysis**

Statistical analyses were performed using IBM SPSS Statistics Version 21. Approximately 7% of data were missing at random (Little’s MCAR $\chi^2(15)=27.86, P=0.02$) and expectation maximization was used to impute missing values. The expectation maximization method was chosen due to the small number of missing data in the sample, and because this method produces unbiased estimates for data that are not missing completely at random (MCAR) (SPSS Inc, 1989). Data are presented as proportions, mean±SD or median [inter-quartile range, IQR] for non-normal variables.

Differences between demographic and clinical variables in individuals with and without

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3 This sentence was added to this Chapter on examiner request, and was not included in the published manuscript.
L-MDD and/or L-GAD were assessed using χ² or independent-samples Student’s t-tests, or Mann-Whitney U or Kruskall-Wallis tests for non-parametric data. Any variable for which there was a significant between-group difference was then included as a covariate in ANCOVA models that examined the independent and combined contribution of L-MDD and L-GAD to current severity of depression and anxiety symptoms.

Indirect mediation models (Hayes, 2013) were then developed to investigate the relationship between L-MDD/L-GAD and HbA₁c, BMI, smoking status and SMBG (see figure in Table 2). Given the expected association between lifetime history and more severe current mood symptoms, we tested whether the relationship between L-MDD/L-GAD and diabetes management may occur indirectly, i.e. whether L-MDD/L-GAD is associated with more severe current depression or anxiety symptoms (path a) which in turn predicts worse diabetes management and control (path b). This is known as the mediation or indirect effect (path ab). We then investigated whether lifetime history directly predicted any outcome of interest (the direct effect or path c’), after accounting for the effect of current mood symptoms. The total effect (path c) reflects the overall strength of the relationship between lifetime history and diabetes management/control, and can be separated into the direct and indirect effect. Bootstrapped bias-corrected 95% confidence intervals (CI) using 5,000 bootstrap samples (Hayes & Preacher, 2014) were calculated, and the indirect effects were significant if these confidence intervals did not span zero. Effects are presented as a regression coefficient (B). Given conservative estimates and reduced Type 1 error inflation produced by bootstrapping confidence intervals, our large sample size (Hayes & Scharkow, 2013) and the exploratory nature of
this study, no adjustments were made for multiple comparisons (Rothman, 1990). A two-tailed alpha of 0.05 was used throughout.

**Results**

The 1,549 adults with type 2 diabetes were aged 65.7 (±11.5) years at baseline and 55.6 (±12.2) years at diabetes diagnosis, 52.0% were men, and 22.6% were insulin-treated. Their median diabetes duration was 9.0 [3.0-15.9] years and median HbA1c levels were 6.8 [6.2-7.7]% (51 [44-61] mmol/mol), with an absolute range of 4.0-17.2% (20-164 mmol/mol). Ninety-three percent (1447) of the sample completed the PHQ-9 and 1426 (92.1%) completed the GADS (1416; 91.4% completed both), while 87% (1341) completed the BLDS and 1454 (94.0%) completed the GAD-LT (1335; 86.2% completed both). All four scales were completed by 1,285 (83.0%). The 264 non-completers were more likely to be Aboriginal (24.6% vs. 3.1%, \( p < .001 \)), prescribed insulin (12.2% vs. 4.3%, \( p < .001 \)), and less likely to have received education beyond primary school (80.9% vs. 87.8%, \( p = .004 \)). There were no between group differences in age (65.5±12.9 years vs. 65.8±11.2, \( p = .83 \)), disease duration (10 [3.0-17.0] vs 8.3[2.5-15.7] years, \( p = .09 \)), or gender (47.4% vs. 51.1%, \( p = .27 \)).

**Overall prevalence of depression and anxiety**

Mild-severe depressive symptoms were reported by 34.2% of the sample and 15.7% were taking antidepressant medication at baseline. A graphic representation of the prevalence and overlap in current and lifetime depression and anxiety diagnoses is shown in Figure 1.
Impact of lifetime depression and/or anxiety on current mood symptoms

Table 1 shows demographic and clinical characteristics of the FDS2 cohort by lifetime depression and/or anxiety status. People with L-MDD only or L-MDD+L-GAD had higher BMI, were younger, and were more likely to be female, unmarried, to smoke and be on antidepressants, than those with no history of that disorder or combination of disorders. L-GAD was associated with increased antidepressant use only, but did not independently impact on clinical characteristics.

After controlling for age, gender, and marital status, ANCOVA models revealed that L-MDD and L-GAD alone were each independently and strongly associated with more severe current depression (L-MDD: $F(1,1291)=297.21$, $P<0.001$, partial $\eta^2=0.19$; L-GAD: $F(1,1385)=267.31$, $P<0.001$, partial $\eta^2=0.16$) and anxiety symptoms (L-MDD: $F(1,1285)=305.32$, $P<0.001$, partial $\eta^2=0.20$; L-GAD: $F(1,1385)=371.66$, $P<0.001$, partial $\eta^2=0.21$). In combination, comorbid L-MDD+L-GAD further elevated the severity of anxiety ($F(1,1390)=329.89$, $P<0.001$, partial $\eta^2=0.19$) and depression symptoms ($F(1,1396)=222.26$, $P<0.001$, partial $\eta^2=0.14$), relative to having either disorder alone, or no history (all $P<0.001$).
Figure 1. Representation of the overlap in prevalence of current (a) and lifetime (b) MDD and GAD.
Table 1.

**Demographic, clinical and mood characteristics by lifetime history of depression and anxiety (N = 1335)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>L-MDD only</th>
<th></th>
<th>p-value</th>
<th>L-GAD only</th>
<th></th>
<th>p-value</th>
<th>L-MDD+LGAD</th>
<th></th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td></td>
<td>Yes</td>
<td>No</td>
<td></td>
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<tr>
<td>Demographic, clinical and self-management characteristics (N = 1335)</td>
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</tr>
<tr>
<td>Number (%)</td>
<td>174 (17.6)</td>
<td>816 (82.4)</td>
<td>&lt;0.001</td>
<td>68 (7.7)</td>
<td>816 (92.3)</td>
<td>0.35</td>
<td>277 (25.3)</td>
<td>816 (74.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age at assessment (years)</td>
<td>62.2±11.3</td>
<td>67.3±10.9</td>
<td>&lt;0.001</td>
<td>66.9±9.8</td>
<td>67.4±11.0</td>
<td>0.35</td>
<td>61.5±10.6</td>
<td>66.7±11.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age at diabetes diagnosis (years)</td>
<td>52.7±11.7</td>
<td>57.0±16.0</td>
<td>&lt;0.001</td>
<td>57.1±11.8</td>
<td>57.1±11.7</td>
<td>0.87</td>
<td>52.3±11.4</td>
<td>56.4±12.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (% women)</td>
<td>57.6</td>
<td>42.8</td>
<td>&lt;0.001</td>
<td>44.6</td>
<td>42.2</td>
<td>0.65</td>
<td>56.3</td>
<td>45.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-fluent in English (%)</td>
<td>8.2</td>
<td>11.3</td>
<td>0.69</td>
<td>9.2</td>
<td>10.9</td>
<td>0.52</td>
<td>6.5</td>
<td>11.1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Education (% beyond primary level)</td>
<td>87.7</td>
<td>87.2</td>
<td>0.35</td>
<td>89.1</td>
<td>87.6</td>
<td>0.88</td>
<td>89.7</td>
<td>86.6</td>
<td>0.18</td>
</tr>
<tr>
<td>Married/partner (%)</td>
<td>56.1</td>
<td>67.7</td>
<td>&lt;.05</td>
<td>70.8</td>
<td>67.3</td>
<td>0.59</td>
<td>56.3</td>
<td>65.7</td>
<td>&lt;0.05</td>
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<tr>
<td>Diabetes duration (years)</td>
<td>10.8</td>
<td>9.0</td>
<td>0.61</td>
<td>9.0</td>
<td>9.0</td>
<td>0.46</td>
<td>7.0</td>
<td>9.0</td>
<td>0.06</td>
</tr>
<tr>
<td>Alcohol use (standard drinks/day)</td>
<td>0.1</td>
<td>0.1</td>
<td>0.05</td>
<td>0.1</td>
<td>0.1</td>
<td>0.27</td>
<td>0.1</td>
<td>0.1</td>
<td>0.17</td>
</tr>
<tr>
<td>HbA1c % (mmol/mol)</td>
<td>7.0 (53)</td>
<td>6.8 (51)</td>
<td>0.15</td>
<td>6.6 (49)</td>
<td>6.8 (51)</td>
<td>0.30</td>
<td>6.8 (51)</td>
<td>6.8 (51)</td>
<td>0.80</td>
</tr>
<tr>
<td>Taking antidepressants (%)</td>
<td>15.5</td>
<td>7.1</td>
<td>&lt;0.001</td>
<td>2.9</td>
<td>7.4</td>
<td>0.17</td>
<td>16.2</td>
<td>8.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>32.6±6.4</td>
<td>30.8±5.9</td>
<td>&lt;0.001</td>
<td>30.6±5.5</td>
<td>30.8±5.9</td>
<td>0.93</td>
<td>32.1±6.6</td>
<td>31.1±6.1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Taking antidepressants (%)</td>
<td>28.3</td>
<td>7.9</td>
<td>&lt;0.001</td>
<td>19.1</td>
<td>7.0</td>
<td>&lt;0.001</td>
<td>33.2</td>
<td>10.0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
**Depression and Anxiety in T2DM**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>L-MDD only</th>
<th>L-GAD only</th>
<th>L-MDD+LGAD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>p-value</td>
</tr>
<tr>
<td>Number (%)</td>
<td>170 (17.6)</td>
<td>796 (82.4)</td>
<td>65 (7.5)</td>
</tr>
<tr>
<td>PHQ-9 total score</td>
<td>4.0</td>
<td>1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GADS total score</td>
<td>6.0</td>
<td>3.0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Note. HbA1c = glycated hemoglobin; PHQ-9 = Patient Health Questionnaire-9 item version; GADS = Generalized Anxiety Disorder Scale; L-MDD = lifetime major depressive disorder; L-GAD = lifetime generalized anxiety disorder; L-MDD+L-GAD = comorbid lifetime major depression and generalized anxiety disorders; data presented are unadjusted for multiple comparisons.

*Of the 1335 participants who completed both the L-MDD and L-GAD questionnaires, 1285 also completed both the PHQ-9 and GADS.
**Impact of lifetime depression and/or anxiety on diabetes behaviours and control**

Mediation models were used to explore whether L-MDD and L-GAD directly (path $c'$) affected BMI, HbA$_{1c}$, smoking status and SMBG or whether the effect was indirectly mediated by the severity of PHQ-9 and GADS scores (path $ab$). Age, gender and marital status were included as covariates in each model. Table 2 includes significant mediation models and non-significant models are presented in Table A1.

As can be seen in model 1, lifetime major depression (L-MDD) was indirectly associated with higher HbA$_{1c}$ levels, via its effect on current depressive symptoms (path $ab_1$: $B = 0.13$, $p < 0.05$). That is, the presence of L-MDD was associated with more severe current depression symptoms (path $a$: $B = 3.16$, $p < 0.001$), which in turn predicted higher HbA$_{1c}$ (path $b$: $B = 0.04$, $p < 0.05$). L-MDD also indirectly predicted less frequent SMBG, by increasing the severity of current depressive symptoms (model 2; path $ab_1$). Conversely, L-MDD was found to be directly associated with higher BMI (model 3, path $c'$) and a greater likelihood of currently smoking (model 4, path $c'$), after accounting for the effect of current depression and anxiety severity.

When considering L-GAD, there was no direct effect of L-GAD on any outcome of interest. However, L-GAD was indirectly associated with higher BMI via its effect on current depressive symptoms (model 5; path $ab_1$). The presence of L-GAD was associated with more severe current depression symptoms (path $a$), which in turn predicted higher BMI (path $b$).
### Table 2.
Indirect mediation models testing the direct (path c’) and indirect (path ab) effect of lifetime depression and anxiety on diabetes management/control, via the severity of current mood symptoms. Data are presented as regression coefficients (B; 95% confidence interval)

![Diagram of mediation models]

<table>
<thead>
<tr>
<th>Model</th>
<th>Predictor</th>
<th>Mediator</th>
<th>Outcome</th>
<th>Path a</th>
<th>Path b</th>
<th>Path ab: Indirect effect of L-MDD/L-GAD on outcomes</th>
<th>Path c: Total effect of L-MDD/L-GAD on outcomes</th>
<th>Path c’: Direct effect of L-MDD/L-GAD on outcomes, accounting for current mood severity</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>L-MDD</td>
<td>PHQ-9 score_1</td>
<td>HbA1c</td>
<td>B₁ = 3.16‡ B₁ = 0.04†</td>
<td>B₁ = 0.13† (0.02 to 0.27)</td>
<td>B = 0.04</td>
<td>B = -0.05</td>
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<td></td>
<td></td>
<td>GADS score_2</td>
<td></td>
<td>B₂ = 3.18‡ B₂ = -0.01</td>
<td>B₂ = -0.04 (-0.15 to 0.07)</td>
<td></td>
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<tr>
<td>2</td>
<td>L-MDD</td>
<td>PHQ-9 score_1</td>
<td>Self-monitoring of blood glucose</td>
<td>B₁ = 3.05‡ B₁ = -0.09†</td>
<td>B₁ = -0.29† (-0.52 to -0.08)</td>
<td>B = -0.38</td>
<td>B = -0.24</td>
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<tr>
<td></td>
<td></td>
<td>GADS score_2</td>
<td></td>
<td>B₂ = 3.06‡ B₂ = 0.05</td>
<td>B₂ = 0.17 (-0.01 to 0.40)</td>
<td></td>
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<tr>
<td>3</td>
<td>L-MDD</td>
<td>PHQ-9 score_1</td>
<td>BMI</td>
<td>B₁ = 3.22‡ B₁ = 0.19†</td>
<td>B₁ = 0.60† (0.07 to 1.16)</td>
<td>B = 1.62†</td>
<td>B = 1.14†</td>
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<td></td>
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<td>GADS score_2</td>
<td></td>
<td>B₂ = 3.21‡ B₂ = -0.04</td>
<td>B₂ = -0.12 (-0.54 to 0.38)</td>
<td></td>
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<tr>
<td>4</td>
<td>L-MDD</td>
<td>PHQ-9 score_1</td>
<td>Smoking status</td>
<td>B₁ = 3.15‡ B₁ = 0.07</td>
<td>B₁ = 0.22 (-0.07 to 0.53)</td>
<td>B = 0.91‡</td>
<td>B = 0.81†</td>
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<td></td>
<td></td>
<td>GADS score_2</td>
<td></td>
<td>B₂ = 3.15‡ B₂ = -0.04</td>
<td>B₂ = -0.13 (-0.45 to 0.13)</td>
<td></td>
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</tr>
<tr>
<td>Model</td>
<td>Predictor</td>
<td>Mediator</td>
<td>Outcome</td>
<td>Path a</td>
<td>Path b</td>
<td>Path ab: Indirect effect of L-MDD/L-GAD on outcomes</td>
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<tr>
<td>5</td>
<td>L-GAD</td>
<td>BMI</td>
<td></td>
<td>B₁ = 1.42‡</td>
<td>B₁ = 0.21†</td>
<td>B₁ = 0.30† (0.05 to 0.77)</td>
<td>B = -0.24</td>
<td>B = -0.26</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>B₂ = 3.50‡</td>
<td>B₂ = -0.08</td>
<td>B₂ = -0.28 (-0.84 to 0.16)</td>
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<tr>
<td></td>
<td></td>
<td>GADS score</td>
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<td></td>
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</tr>
<tr>
<td>6</td>
<td>L-MDD+L-GAD</td>
<td>PHQ-9 score</td>
<td>HbA₁c</td>
<td>B₁ = 5.70‡</td>
<td>B₁ = 0.03†</td>
<td>B₁ = 0.19† (0.04 to 0.35)</td>
<td>B = -0.08</td>
<td>B = -0.25</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>B₂ = 6.33‡</td>
<td>B₂ = -0.00</td>
<td>B₂ = -0.03 (-0.18 to 0.11)</td>
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<tr>
<td>7</td>
<td>L-MDD+L-GAD</td>
<td>PHQ-9 score</td>
<td>Self-monitoring of blood glucose</td>
<td>B₁ = 5.70‡</td>
<td>B₁ = -0.06†</td>
<td>B₁ = -0.36† (-0.67 to -0.07)</td>
<td>B = -0.46†</td>
<td>B = -0.24</td>
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<td></td>
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<td></td>
<td>B₂ = 6.28‡</td>
<td>B₂ = 0.02</td>
<td>B₂ = 0.15 (-0.15 to 0.53)</td>
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<tr>
<td>8</td>
<td>L-MDD+L-GAD</td>
<td>PHQ-9 score</td>
<td>BMI</td>
<td>B₁ = 5.73‡</td>
<td>B₁ = 0.27†</td>
<td>B₁ = 1.56† (0.93 to 2.29)</td>
<td>B = 0.32</td>
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<td>B₂ = 6.35‡</td>
<td>B₂ = -0.08</td>
<td>B₂ = -0.49 (-1.23 to 0.16)</td>
<td></td>
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</tr>
<tr>
<td>9</td>
<td>L-MDD+L-GAD</td>
<td>PHQ-9 score</td>
<td>Smoking status</td>
<td>B₁ = 5.70‡</td>
<td>B₁ = 0.08†</td>
<td>B₁ = 0.47† (0.08 to 0.88)</td>
<td>B = 0.26</td>
<td>B = -0.01</td>
</tr>
<tr>
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<td></td>
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<td></td>
<td>B₂ = 6.32‡</td>
<td>B₂ = -0.04</td>
<td>B₂ = -0.23 (-0.70 to 0.19)</td>
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</tr>
</tbody>
</table>

Note. L-MDD = lifetime major depressive disorder; L-GAD = lifetime generalized anxiety disorder; L-MDD+L-GAD = both lifetime major depression and generalized anxiety disorders; PHQ-9 = Patient Health Questionnaire-9 item version; GADS = Generalized Anxiety Disorder Scale; B = regression coefficient; a = association between the L-MDD/L-GAD and current mood symptoms; b = association between current depression/anxiety symptom severity and diabetes outcomes; ab = test of the indirect effect of lifetime history on outcomes via current mood symptom severity; c = total effect of L-MDD/L-GAD on the outcome variable (path ab + path c’); c’ = direct effect of L-MDD/L-GAD on the outcome variable, after accounting for the current mood symptom severity. 1 = PHQ-9 scores as the mediator; 2 = GADS scores as the mediator; † p < .05. ‡ p < .001.
Finally, comorbid L-MDD+L-GAD were indirectly associated with all of the outcomes of interest (models 6-9, significant path ab1). L-MDD+L-GAD were significantly associated with higher HbA$_{1c}$, BMI, smoking and less frequent SMBG, by increased severity of current depression symptoms. Of note, current anxiety symptom severity was not a significant mediator in any model.

**Discussion**

The results of the present large, community-based prospective study show that lifetime depression and anxiety are significant risk factors for adverse psychological outcomes, poorer health behaviour and worse glycaemic control in type 2 diabetes. As previously demonstrated (Marcus et al., 1992), L-MDD was associated with more severe current depressive symptoms but, for the first time, this finding was replicated for people with L-GAD. L-GAD was present in approximately one quarter of our sample and was significantly associated with more severe anxiety and depressive symptoms. Notably, L-MDD had a marked impact on diabetes management. L-MDD alone was directly associated with greater likelihood of current smoking and a higher BMI, and indirectly associated with higher HbA$_{1c}$ and reduced SMBG. L-GAD alone was indirectly related to higher BMI only through increased severity of current depression. These findings indicate that the presence of a history of major depression in particular, is an important early indicator of individuals at elevated risk of later psychological symptomatology and worse diabetes management and glycaemic control.

These findings partially support those of Wagner and colleagues (Wagner et al., 2010) who reported a direct association between L-MDD and higher HbA$_{1c}$ levels for women without current depression. The present study found this relationship to be fully explained by the severity of current depressive symptoms, as was the effect of L-MDD
on SMBG. This suggests that, when present, current mood problems may play an equal or greater role than lifetime depression in influencing glycaemic control. Instead, L-MDD directly impacted on BMI and smoking status, which may be explained in part by the chronicity of behaviours associated with smoking and overweight. Major depression is a known risk factor for smoking and higher BMI, which tend to be more long-standing issues and can increase the risk of developing diabetes (Katon, 2003). Importantly, all assessed outcomes and behaviours in this study have been linked to increased risk of adverse health outcomes and micro- and macrovascular complications (Bruce et al., 2013; E. H. B. Lin, Katon, Michael Von, Rutter, & et al., 2004).

There has been no previous investigation of the overlap in lifetime depression and anxiety in type 2 diabetes. Of considerable clinical importance is our finding that the combination of L-MDD+L-GAD confers additional risk for more severe psychological symptoms, higher BMI, worse glycaemic control, and increased likelihood of smoking, than either disorder in isolation. These individuals were more likely to be women, younger in age, and unmarried. This finding extends our previous study (Starkstein et al., 2014) in which higher overlap in MDD and GAD was associated with the worst outcomes. When presenting together, MDD and GAD are associated with reduced remission in both disorders over time (Schoevers et al., 2005) and are recurrent conditions in individuals with diabetes (Fisher et al., 2008). We suggest, therefore, that there is screening for L-MDD and L-GAD at diabetes diagnosis, particularly in younger, unmarried women, to identify individuals requiring earlier primary care or specialist intervention, and/or more regular symptom monitoring. This is especially relevant when individuals may not present with elevated mood symptoms within the first year following diabetes diagnosis (Skinner et al., 2010). Identification of whether individuals
developed depression/anxiety prior to or following diabetes onset, may also help inform the most appropriate intervention (Bruce et al., 2013). Finally, routine monitoring of depression symptoms in diabetes, especially for more at-risk individuals, provides another important avenue for faster identification of worsening of symptoms and more targeted treatment to improve long-term psychiatric and health outcomes.

The present study had some limitations. First, mediation analysis requires a temporal relationship between the independent variable, mediator, and outcome. As this study was cross-sectional, conclusions regarding the direction of the relationship between psychological symptoms and diabetes control and behavior are thus tentative. Longitudinal follow-up of this cohort is ongoing, and will allow for stronger evidence regarding the causal nature of these relationships. Second, assessment of depression and anxiety disorders using gold standard structured clinical interviews was beyond the scope of the present study. This methodology is not often feasible in large, community based studies, and self-report measures of mood symptoms are frequently used to screen for depression and anxiety (T. Roy, Lloyd, Pouwer, Holt, & Sartorius, 2012). We used the PHQ-9, a valid and reliable instrument for assessing depression symptoms and potential diagnosis (Kroenke & Spitzer, 2002; Spitzer et al., 1999), and the GADS, which was designed to map directly on to DSM-IV criteria for GAD (Starkstein et al., 2014), with both measures demonstrating high concordance with diagnostic interview (Spitzer et al., 1999; Starkstein et al., 2014). The Generalized Anxiety Disorder 7-item scale (GAD-7) was not used in the present study as it was not available when the study

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4 This sentence was added to this Chapter on examiner request, and was not included in the published manuscript.
5 This sentence was added to this Chapter on examiner request, and was not included in the published manuscript.
was designed. As previously reported, we believe the GADS is an improvement on the GAD-7 as it assesses all DSM-IV/5 criteria for GAD over the past 6 months, while the GAD-7 assesses a partial list of symptoms over the past 2 weeks (Starkstein et al., 2014). Without partialling out the effect of the other disorder, the prevalence of current MDD (5.7%), GAD (6.5%), L-MDD (29.2%) and L-GAD (23.0%) in the present study were also equivalent to, or less than, those seen in other studies (Gonzalez, Peyrot, et al., 2008; Grigsby et al., 2002; Starkstein et al., 2014) suggesting no issues with over-diagnosis. However, symptoms of depression and anxiety assessed by the PHQ-9 and GADS such as loss of energy, poor appetite, and overeating can be confounded with the symptoms of poorly managed diabetes (T. Roy et al., 2012); thus it is possible that these self-report measures may overestimate the prevalence of psychological symptoms in this population. This is a common issue faced when assessing mood symptoms in chronically ill populations, and while measures often separate items into cognitive or somatic categories to address this problem, it is generally agreed that adopting an inclusive approach and measuring all mood symptoms is preferred⁶.

Third, multiple comparisons performed when running the indirect mediation models may inflate type 1 error. However, this is more likely to occur for multi-categorical rather than binary (Yes/No) predictor variables (Hayes & Preacher, 2014). Further, we applied 95% bias-corrected bootstrapped confidence intervals which is recommended practice for providing conservative estimates with a reduced risk of error (Hayes, 2013). Finally, we did not assess diabetes-related distress, which has also been shown to impact on diabetes management (Fisher et al., 2008, 2010; Gonzalez, Peyrot, 

⁶These two sentences were added to this Chapter on examiner request, and were not included in the published manuscript.
et al., 2008). Elevated levels of distress may account for some of the relationship between depression, anxiety and diabetes management and control in the present study.

In conclusion, a history of anxiety, depression or both significantly increases the risk of the later symptomatic experience of these disorders and adverse glycaemic control and behavioural management. The most important clinical implication of our data is the need to consider the impact of both lifetime depression and anxiety on how individuals with type 2 diabetes present currently, and the potential implications for long-term health. We suggest that, through earlier identification and treatment of long-standing depression and anxiety, the later risk of more severe psychological symptomatology, worse glycemic control, and associated risk for health complications, may be reduced.
Chapter 3: Dealing with Missing Data in Longitudinal Analysis

Preface

Chapter 2 of this thesis outlined the contribution of lifetime MDD and GAD to psychological symptom severity and diabetes management, in a cross-sectional design. The next Chapter (Study 2) extends these findings by considering the course and pattern of depression symptoms longitudinally in this population. As a preliminary step in data analysis for Study 2, a number of methodological considerations were taken into account to ensure the accuracy of analyses and to account for discrepancies in how data were collected. Of particular interest, a primary problem in conducting longitudinal studies is missing data (Enders, 2010; H. Lin, McCulloch, & Rosenheck, 2004), which can frequently occur when individuals are followed up over multiple assessment points for a number of years. This Chapter outlines common types of missing values observed in longitudinal datasets, and the application of three longitudinal modeling techniques to addressing these issues in the FDS2 depression data: missing at random; pattern-mixture; and, selection-modeling (Enders, 2010; B. O. Muthén, Asparouhov, Hunter, & Leuchter, 2011).
Types of missing data

Three types of missing data are widely recognized in the literature. Firstly, data can be missing due to another variable in the dataset (missing at random; MAR), missingness can be completely unrelated to the data (missing completely at random; MCAR), or missingness can be related to the variable of interest itself (not missing at random; NMAR, Enders, 2010). Taking depression as an example, males, or those with less English fluency, may be less likely to complete a self-report measure of their symptoms (e.g. on the Patient Health Questionnaire-9; PHQ-9, Kroenke & Spitzer, 2002) leading to the data being MAR. Alternatively, the variable of interest itself, in this case depression, may impact on completion of the PHQ-9 at later time points: for example those who are more depressed may be more likely to drop-out of a study, or fail to complete the PHQ-9 without support (e.g. at home, compared to with a researcher when attending an appointment; NMAR). Within these types of missing data, missing values can also be systematic or intermittent in nature. There may be a systematic pattern to individuals’ who drop-out of the study (e.g. those who are more depressed drop out earlier), or individuals may come and go throughout a study and have missing data at some time points but continue to participate (termed intermittent missingness; H. Lin et al., 2004). The type of missing data will determine how missingness is accounted for in further analyses, and the context in which results are interpreted.

The following sections outline a) missing values analysis performed to determine the nature of missing depression data7, b) modeling techniques employed to address the

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7 Missingness was not a problem for GADS anxiety data, so this is dealt with in Chapter 5.
issue of missingness in Study 2, and c) methodological implications for future longitudinal research.

**Data collection and study procedures**

The assessment of depression symptoms throughout this thesis was performed using the PHQ-9 (Kroenke & Spitzer, 2002). As stated in Study 1, this measure has high sensitivity to change in depression over time (Löwe, Kroenke, Herzog, & Gräfe, 2004), good diagnostic concordance with clinical interview (Spitzer et al., 1999), and is validated for use in type 2 diabetes (Lin, Katon, Von Korff, Rutter, & et al., 2004; van Steenbergen-Weijenburg et al., 2010). The PHQ-9 was collected at a maximum of 6 occasions for individuals entering the study between 2008 and 2011. This measure was completed at face-to-face assessment when patients attended for baseline (Year 0) or biennial interview, at 2-year (Year 2), and 4-year (Year 4) follow-up at Fremantle Hospital. In the intervening years, the questionnaire was mailed to participants (Years 1, 3, and 5) and returned via reply-paid envelope. Complete data at all 6 time points were available for 195 participants, 294 had complete data at 5 time points, 225 at 4, 269 at 3, 218 at 2, and 288 participants had data at one time point only.

**Missing Values Analysis**

To determine the amount and nature of missing data on the PHQ-9, missing values analyses were performed in IBM SPSS Statistics Version 23. At the first stage, analyses were performed at the item-level to examine patterns of missing items on the PHQ-9 at each visit. This was performed for individuals with 8 or fewer missing items, as individuals with 9 missing items had not completed the scale. At the second stage, analyses were performed at the scale-level to examine patterns of drop-out and scale non-completion over time.
**Item-level missing values analysis**

At each time point, the Little’s MCAR statistic was calculated to examine patterns of missingness with a non-significant $p$-value indicating that items were missing completely at random (MCAR). Little’s MCAR was significant at Year 0, $\chi^2 = 188.70, p < .001$, Year 1, $\chi^2 = 243.57, p = .004$, Year 3, $\chi^2 = 342.72, p < .001$, and Year 5, $\chi^2 = 211.90, p < .001$, suggesting that items were not missing completely at random. However, as there was less than 5% missingness on items of the PHQ-9 at each time point, examination of factors related to item missingness was not performed. Following recommendations (Enders, 2010; SPSS Inc, 1989) expectation maximization (EM) estimation was then employed to impute missing values for individuals with up to 3 missing items on the PHQ-9. Individuals with 4 or more missing items on the PHQ-9 at any time point were excluded, as valid total scores could not be calculated. The resultant scale totals were used for all subsequent analyses.

**Scale-level missing values analysis**

To examine factors associated with non-completion of the PHQ-9 longitudinally, missing values analyses were performed using the scale totals derived following EM imputed data for item scores, at each time point. PHQ-9 total scores for each time point were entered together into the analyses, which revealed that Little’s MCAR was significant, $\chi^2 = 197.38, p = .027$, indicating data were not MCAR. Separate variance $t$-tests revealed that, at certain time-points, non-completion of the PHQ-9 was related to the severity of depressive symptoms at other assessments. Higher PHQ-9 scores at Year 0 were associated with more missingness at Year 2, $t (36.9) = -2.4, p = .023$, and more severe depression symptoms at Year 1 were significantly associated with more missingness at Year 2, $t (802.2) = -3.8, p < .001$, Year 3, $t (135.4) = -4.5, p < .001$, and
Depression and Anxiety in T2DM

Year 4, $t (543.6) = -3.0, p = .003$. Demographic and clinical factors did not significantly affect missingness (all $ps > .05$). Taken together, these data suggest that the severity of individuals’ depression symptoms earlier in this study affected rates of scale non-completion longitudinally. This indicates systematic and non-ignorable missingness in the data and that data were NMAR (Enders, 2010; SPSS Inc, 1989). That is, the probability of a missing PHQ-9 score was dependent on the severity of previous depression scores. The remainder of this Chapter discusses longitudinal modeling approaches designed to deal with NMAR data, and the application of these approaches to PHQ-9 data in Study 2.

**Longitudinal methods for modeling missing data**

The primary research aim of Study 2 was to investigate how depression symptoms, as assessed by the PHQ-9, develop and change over the course of type 2 diabetes. Therefore, a modeling approach that addresses this question in addition to incorporating longitudinal NMAR data will be discussed for the remainder of this Chapter.

To examine the course and pattern of depression symptoms over time, latent curve growth analysis (LCGA) was performed using *Mplus* Version 7 (L. K. Muthén & Muthén, 1998). This analysis investigates whether there are unobserved sub-groups (classes) of individuals who show similar patterns of change on an outcome of interest (e.g. PHQ-9 scores) over time, and estimates the probability of each individual belonging to a particular class (Jung & Wickrama, 2008; Ram & Grimm, 2009). LCGA then determines the number of classes or groups that best fit the data, and best represent the pattern of change in that variable over time. Within the LCGA model, there are three primary approaches which apply different methodologies to incorporating missingness;
the missing at random (MAR) model, pattern-mixture model (PMM) and Diggle-Kenward selection-model (Diggle-Kenward SM). Although data for this Chapter are assumed to be NMAR, the MAR model is discussed in order to address the underlying differences between this approach and those models designed specifically for NMAR data.

**Missing at random (MAR) modeling.** The MAR model is the most commonly performed modeling procedure for longitudinal curve growth analyses. This approach incorporates systematic missingness into model development, whereby the likelihood of missing data at Year $x$ can relate to depression scores from previous assessments (Enders, 2011b). In *Mplus*, the MAR model is estimated using Full Information Maximum Likelihood (FIML) estimation. Strengths of the FIML procedure are that this approach uses all available data to generate parameter estimates (Enders, 2010; Enders & Bandalos, 2001) rather than excluding incomplete cases or missing values, and in doing so maximizes the amount of data included. However, MAR models do not account for non-ignorable missingness, which is incorporated into the following two models.

**Pattern-mixture modeling (PMM).** PMM incorporates missingness by separating the sample into subgroups of individuals who share similar missing data patterns (Enders, 2011). For example, individuals who all drop out after Year 1 may share pattern $a$, all those who drop-out after Year 3 share pattern $b$, and all individuals who complete the PHQ-9 at Year 0, 2, and 4 only (e.g. when assessed in person at interview) would share pattern $c$. Then, PMM models a single growth curve and unique model estimates for each pattern, and combines these to produce average estimates and standard errors for the overall model (Enders, 2011a). This method assumes that subjects in each pattern share a common response distribution. However, this assumption has
been criticized (J. Roy, 2003), as individuals within each pattern may drop out for many reasons, and where there are multiple patterns these may have small samples which bias estimates. To account for this, the Roy latent dropout pattern-mixture model (Roy-PMM) has been proposed. This method uses a latent class variable that is influenced by dropout time, and influences the random effect for the outcomes (B. O. Muthén et al., 2011). That is, Roy-PMM assumes class membership is unknown (J. Roy, 2003) and that class membership is related to, but separate from, dropout times. In doing so, this model views the formation of latent subgroups as a better dropout classification of subjects than using observed dropout time (B. O. Muthén et al., 2011; J. Roy, 2003), as in traditional PMM.

**Selection-modeling (SM).** Selection models, instead, deal with NMAR data by combining a growth curve model with a set of regression equations that predict missingness (Enders, 2011a). These models relate the probability of missing data at time \( t \) to the outcome variable at time \( t \) (and at previous assessments; Enders, 2011). In doing so, selection models such as the Diggle-Kenward model, allow modeling of the relationships between the outcome variable across visits and the influence of proceeding measures of outcomes on later missingness. The repeated measures variables predict the probability of missing data at a particular wave (Enders, 2011a), thus accounting for non-ignorable dropout and intermittent missingness. Similar to PMM, a number of difficulties in running these models have been highlighted. This includes the assumption of multivariate normality, meaning that even small deviations from normality in the data can bias the model (Enders, 2011a).
Application of NMAR modeling approaches to PHQ-9 data

As missing values analyses in SPSS revealed that the PHQ-9 data were NMAR over time, Muthén and colleagues’ (B. O. Muthén et al., 2011) recommendations for dealing with non-ignorable dropout were followed. Given the aforementioned limitations of each method in modeling missingness, Muthén et al. (2011) recommend running MAR, PMM, Roy-PMM, and Diggle-Kenward SM methods and comparing results to determine the best approach to the data (B. O. Muthén et al., 2011). If all approaches agree, then the MAR model can be considered supported (B. O. Muthén et al., 2011). However, if the MAR model differs to the PMM and Diggle-Kenward SM models’ in substantive ways, then NMAR results may better reflect the data. Finally, if all three approaches differ, all results should be presented, as there is no statistical basis for preferring one method of modeling to another.

Statistical analyses

At the first step, to determine the best fitting number of classes for each method, LCGA for each of the above modeling techniques was run with 2-4 classes and a quadratic fit. A conventional 1-class MAR model was also generated as a comparison (B. O. Muthén et al., 2011). The best fitting number of classes within each method was decided based on a combination of the following fit indices: the Bayesian Information Criterion (BIC) which measures goodness of fit and model parsimony, where lower scores indicate better fit (Jung & Wickrama, 2008); the Vuong-Lo-Mendell-Rubin Likelihood Ratio Test (LRM-LRT), with significant values indicating improvement in model fit when adding an extra class compared to the previous model (Lo, Mendell, & Rubin, 2001); high entropy (near 1.0), considered to reflect good precision of the model in classifying individuals to each class (Jung & Wickrama, 2008; Nagin, 2005); and the
percentage of individuals in each class, with less than 5% in any given class considered too small and suggesting exclusion of that class.

At the second step, the best fitting number of classes for each method was compared based on the shape of growth curves generated and the number of individuals who were classified into each group. This allows for exploration of whether non-ignorable/intermittent missingness of the PHQ-9 data had an influence on the latent growth curves generated in the MAR model, relative to when estimated using approaches developed to account for NMAR data. The final method for modelling longitudinal PHQ-9 data was chosen based on the degree of similarity or difference between all models, in addition to computational burden, parsimony and model interpretability (B. O. Muthén et al., 2011; Ram & Grimm, 2009).

Results

Of the 1549 individuals recruited to the FDS2 with clinically diagnosed type 2 diabetes, 1505 had PHQ-9 data at 1 or more time points and were thus included in the LCGA. Tables 3-5 below present the model fit indices for the MAR, PMM, and Roy-PMM models. Given the complexity and computational burden of selection-modeling procedures (Enders, 2011b), the Diggle-Kenward SM 2-4 class models did not converge and produced biased estimates. Unbiased models were unable to be generated, and therefore the results of these models could not be trusted and have not been reported here.

As can be seen in Table 3-5, there was agreement across the MAR, PMM and Roy-PMM models that a 4-class solution had the lowest BIC value, suggesting best fit. However, for all models, the 4-class solution did not significantly improve model fit beyond the 3-class model (LRM-LRT \( p > .05 \)) and the fourth class comprised fewer than
5% of the sample. Based on a combination of these model fit indices, parsimony and interpretability of the model, a 3-class solution was chosen for each method as the best-fitting model for the longitudinal PHQ-9 data.
Table 3.

*LCGA fit statistics for PHQ-9 quadratic missing at random (MAR) model with 1-4 classes*

<table>
<thead>
<tr>
<th>Class size</th>
<th>1-Class</th>
<th>2-Class</th>
<th>3-Class *</th>
<th>4-Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 1</td>
<td>1505 (100%)</td>
<td>1329 (88.31%)</td>
<td>1277 (84.85%)</td>
<td>1169 (77.67%)</td>
</tr>
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<td>N = 2</td>
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<td>176 (11.69%)</td>
<td>114 (7.58%)</td>
<td>185 (12.29%)</td>
</tr>
<tr>
<td>N = 3</td>
<td>-</td>
<td>-</td>
<td>114 (7.58%)</td>
<td>87 (5.78%)</td>
</tr>
<tr>
<td>N = 4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>64 (4.25%)</td>
</tr>
</tbody>
</table>

Fit Statistics

<table>
<thead>
<tr>
<th># of Parameters</th>
<th>12</th>
<th>16</th>
<th>20</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIC</td>
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<td>28031.51</td>
<td>27814.56</td>
<td><strong>27653.40</strong></td>
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<td>Entropy</td>
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<td>0.897</td>
<td>0.879</td>
</tr>
<tr>
<td>Log likelihood</td>
<td>-14207.65</td>
<td>-13957.23</td>
<td>-13834.11</td>
<td>-13738.90</td>
</tr>
<tr>
<td>LRM-LRT p value</td>
<td>-</td>
<td>0.012</td>
<td>0.002</td>
<td>0.124</td>
</tr>
</tbody>
</table>

*Note. Lowest BIC value is in boldface. BIC = Bayesian Information Criterion (lower score = better fit); LRM-LRT = Vuong-Lo-Mendell-Rubin Likelihood Ratio Test (significant p value = improvement in model fit). *
* Preferred model.
Table 4.

*LCGA fit statistics for PHQ-9 quadratic pattern mixture model (PMM) with 2-4 classes*

<table>
<thead>
<tr>
<th>Class size</th>
<th>2-Class</th>
<th>3-Class*</th>
<th>4-Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 1</td>
<td>1346 (8.94%)</td>
<td>1280 (85.05%)</td>
<td>1163 (77.28%)</td>
</tr>
<tr>
<td>N = 2</td>
<td>159 (10.57%)</td>
<td>116 (7.71%)</td>
<td>191 (12.69%)</td>
</tr>
<tr>
<td>N = 3</td>
<td>-</td>
<td>109 (7.24%)</td>
<td>87 (5.78%)</td>
</tr>
<tr>
<td>N = 4</td>
<td>-</td>
<td>-</td>
<td>64 (4.25%)</td>
</tr>
</tbody>
</table>

**Fit Statistics**

<table>
<thead>
<tr>
<th></th>
<th>2-Class</th>
<th>3-Class</th>
<th>4-Class</th>
</tr>
</thead>
<tbody>
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<td>BIC</td>
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<td><strong>27720.88</strong></td>
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<td>0.880</td>
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<tr>
<td>Log likelihood</td>
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<td>-13826.84</td>
<td>-13728.74</td>
</tr>
<tr>
<td>LRM-LRT p value</td>
<td>0.010</td>
<td>0.004</td>
<td>0.111</td>
</tr>
</tbody>
</table>

*Note. Lowest BIC value is in boldface. BIC = Bayesian Information Criterion (lower score = better fit); LRM-LRT = Vuong-Lo-Mendell-Rubin Likelihood Ratio Test (significant p value = improvement in model fit). *Preferred model.*
Table 5.

*LCGA fit statistics for PHQ-9 quadratic Roy-pattern mixture model (Roy-PMM) with 2-4 classes*

<table>
<thead>
<tr>
<th>Class size</th>
<th>2-Class</th>
<th>3-Class*</th>
<th>4-Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 1</td>
<td>1328 (88.24%)</td>
<td>1267 (84.19%)</td>
<td>1199 (79.67%)</td>
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<tr>
<td>N = 2</td>
<td>177 (11.76%)</td>
<td>124 (8.24%)</td>
<td>130 (8.64%)</td>
</tr>
<tr>
<td>N = 3</td>
<td>-</td>
<td>114 (7.58%)</td>
<td>130 (8.64%)</td>
</tr>
<tr>
<td>N = 4</td>
<td>-</td>
<td>-</td>
<td>46 (3.06%)</td>
</tr>
</tbody>
</table>

Fit Statistics

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<th># of Parameters</th>
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<th>30</th>
<th>39</th>
</tr>
</thead>
<tbody>
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<tr>
<td>Entropy</td>
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<td>0.890</td>
</tr>
<tr>
<td>Log likelihood</td>
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<td>-13811.19</td>
<td>-13717.85</td>
</tr>
<tr>
<td>LRM-LRT p value</td>
<td>0.005</td>
<td>0.006</td>
<td>0.132</td>
</tr>
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</table>

*Note.* Lowest BIC value is in boldface. BIC = Bayesian Information Criterion (lower score = better fit); LRM-LRT = Vuong-Lo-Mendell-Rubin Likelihood Ratio Test (significant p value = improvement in model fit). *Preferred model.*
Table 6 presents a comparison of fit statistics for the 3-class preferred model for MAR, PMM and Roy-PMM models. There was similarity between all 3-class models in terms of model fit and parsimony, as indicated by similar BIC values and high entropy. These models were then compared on similarities in the shape of growth curves for each class, and the proportion of individuals classified to each class. As can be seen in Figure 2, the shapes of growth curves for the 3-class model were similar across methods. Each method of modeling missingness displayed a class with low depression symptoms over time (Class 1), a class with depression symptoms that worsened then began to improve (Class 2), and a class with depression symptoms that began to improve and worsened again (Class 3). There were only slight differences between the percentages of individuals classified into each class across methods. Taken together, these findings indicate agreement between MAR and NMAR (pattern-mixture) methods for modeling missingness, and that the nature of missing depression data observed in this study did not significantly affect model results. The MAR model was therefore supported, and this method is applied to PHQ-9 data in all subsequent Chapters of this thesis.
Table 6.

*LCGA fit statistics for PHQ-9 quadratic MAR, PMM and Roy-PMM 3-class preferred models*

<table>
<thead>
<tr>
<th>Fit Statistics</th>
<th>3-Class MAR</th>
<th>3-Class PMM</th>
<th>3-Class Roy-PMM</th>
</tr>
</thead>
<tbody>
<tr>
<td># of Parameters</td>
<td>20</td>
<td>32</td>
<td>30</td>
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<tr>
<td>BIC</td>
<td>27814.56</td>
<td>27887.80</td>
<td>27841.87</td>
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<tr>
<td>Entropy</td>
<td>0.897</td>
<td>0.896</td>
<td>0.892</td>
</tr>
<tr>
<td>Log likelihood</td>
<td>-13834.11</td>
<td>-13826.84</td>
<td>-13811.19</td>
</tr>
<tr>
<td>LRM-LRT p value</td>
<td>0.002</td>
<td>0.004</td>
<td>0.006</td>
</tr>
</tbody>
</table>

*Note.* BIC = Bayesian Information Criterion (lower score = better fit); LRM-LRT = Vuong-Lo-Mendell-Rubin Likelihood Ratio Test (significant p value = improvement in model fit); MAR = Missing at Random; PMM = Pattern Mixture model.
Figure 2. Mean, estimated PHQ-9 total scores for the preferred 3-class quadratic LCGA models for a) MAR, b) PMM, and c) Roy-PMM models.
Discussion

Missing data are a problem commonly faced by researchers undertaking longitudinal cohort studies, and multiple methods have been proposed to account for this. This Chapter provided an applied example of newly emerging modeling techniques specifically designed to account for systematic and non-ignorable (NMAR) missing data. The findings suggest that, relative to NMAR methods, a MAR model was the most representative and parsimonious fit for the PHQ-9 data, as it was not significantly biased by the nature of missingness in the study. By comparing MAR and NMAR approaches, more informed decisions relating to the nature of missingness and the effect on results are allowed. However, as with all missingness approaches, there are a number of strengths and limitations that also require addressing.

Longitudinal modeling approaches to missingness: strengths and difficulties

MAR and NMAR modeling approaches have a number of strengths that build on the difficulties faced by traditional methods. Traditional methods include listwise or pairwise deletion, which require data to be MCAR (Enders & Bandalos, 2001). Listwise deletion involves excluding any individuals who do not have a complete case for all variables, and pairwise deletion utilizes all available data by deleting cases on a variable by variables basis (Enders & Bandalos, 2001). Both methods can produce biased estimates if data are MAR or NMAR (Enders, 2010) rather than MCAR. Further, analyzing data only for those with complete cases excludes individuals who may have intermittent missing data (e.g. come and go throughout the study but do not drop out),
and those with non-ignorable missingness (e.g. those who dropout as they are more depressed). In doing so, any estimates produced are biased by the samples that remain.

In contrast, MAR and NMAR modeling approaches for dealing with missing data aim to include as many cases as possible and to incorporate predictors of missingness into the model, and are thus significant improvements on earlier methods. These methods have not been widely used in the behavioural research (Enders, 2010) and provide a novel and potentially important avenue for dealing with the complexity of missingness in longitudinal psychological data. However, while NMAR models provide a strong alternative to deletion techniques, these procedures can also be biased by their underlying assumptions. For example, pattern-mixture models involve accurate specification of the values of inestimable parameters, and selection-models rely on the underlying assumption of normality, which is hard to test (Enders, 2010; B. O. Muthén et al., 2011). Further, the Diggle-Kenward method has very heavy computational burden (B. O. Muthén et al., 2011) and, possibly due to underlying non-normality of the present data, produced biased estimates so could not be included in the results of this Chapter.

The potential that selection modeling may have provided a different pattern of findings cannot be ruled out. This difficulty highlights the issues associated with using such methods for dealing with non-ignorable dropout, and that any decision made needs to discuss the potential for bias even after missingness has been accounted for.

**Methodological implications**

The findings of this Chapter provide an example methodology of how to deal with NMAR data in longitudinal modeling. This is one of the few studies to apply
pattern-mixture and selection modeling to a psychological data set, and provides a novel discussion of the decision-making process behind dealing with the complexity of missingness. These approaches, whether they agree or not, provide a significant improvement on deletion methods (Enders, 2010). Specific mechanisms of missing data, for example data that are missing due to the outcome of interest, can be addressed and individuals with intermittent missingness can remain in the study. Further, these methods provide a critical way of testing whether the MAR model is trustworthy for data that are NMAR (B. O. Muthén et al., 2011). However, even when NMAR mechanisms are found, selection and pattern-mixture models may not necessarily be the best solution (Enders, 2010). Therefore, we suggest, based on Muthén et al.’s recommendations (B. O. Muthén et al., 2011), that any decisions made regarding how to incorporate missing data should be based on consideration of all available approaches.

While further research is needed regarding the best application of these approaches to the psychological and behavioural sciences, this Chapter suggests that longitudinal MAR and NMAR modeling approaches provide a useful and methodologically sound method for modeling missing data. The next Chapter of this thesis (Study 2) therefore incorporates this approach into further modeling of longitudinal PHQ-9 data.
Chapter 4: Depression Symptoms Are Persistent In Type 2 Diabetes: Risk Factors And Outcomes Of 5-Year Depression Trajectories Using Latent Class Growth Analysis.

This chapter was published in the journal Diabetic Medicine: Whitworth, S.R., Bruce, D.G., Starkstein, S.E., Davis, W.A., Davis, T.M.E., Skinner, T.C., Bucks, R.S. (2017). Depression symptoms are persistent in type 2 diabetes: risk factors and outcomes of 5-year depression trajectories using latent class growth analysis. Diabetic Medicine; 34; 1108-15. It is presented below, as published, but formatted for consistency with the rest of the thesis.

Preface

A complicating factor in the successful management of depression in T2DM, is the potential fluctuation and interplay between both depression and diabetes over time. While this relationship is known to be bi-directional, longitudinal associations between changes in depression and changes in diabetes-related outcomes are unclear. This Chapter adapted the best-fitting Missing At Random LCGA model for longitudinal PHQ-9 data identified in Chapter 3, to examine demographic, psychological, and diabetes-specific predictors of the course of depression symptoms in T2DM. Associations between the course of depression symptoms, and changes in weight, glycaemic control, and self-management were then explored.
Abstract

Aims: Depression is common in type 2 diabetes and confers a poor prognosis, yet the longitudinal course of depression symptoms in this population is unclear. This study aimed to describe long-term trajectories of depression symptom severity, and to identify predictors and associates of these trajectories.

Methods: A community-dwelling cohort of 1,201 individuals with type 2 diabetes from the Fremantle Diabetes Study-Phase II (FDS2) was followed for 5 years. The PHQ-9 was administered annually to assess depression symptoms, and biomedical and psychosocial measures were assessed at baseline and biennially. Latent class growth analysis was used to identify classes of depression severity trajectories and associated outcomes, and logistic regression models determined predictors of class membership.

Results: Three trajectories of depression symptoms were identified: continuously low depression symptoms (85.2%), gradually worsening symptoms that then began to improve (persistent depression – low-start, 7.3%), and gradually improving symptoms which later worsened (persistent depression – high-start, 7.5%). Younger age, being a woman, and a lifetime history of major depressive disorder, were associated with greater risk of persistent depression symptoms. Persistent depression was associated with consistently higher body mass index (BMI) over time, but not with changes in HbA₁c or self-monitoring of blood glucose (SMBG).

Conclusions: A sub-set of individuals with type 2 diabetes is at risk of depression symptoms that remain elevated over time. Younger, overweight individuals with a
history of depression may benefit from early and intensive depression management and ongoing follow-up as part of routine type 2 diabetes care.
Introduction

Depression is prevalent in type 2 diabetes (Type 2 DM) and results in impaired diabetes self-management, worse glycaemic control, increased healthcare use, and increased complications and mortality (de Groot et al., 2001; Egede et al., 2002; Gonzalez et al., 2007). The relationship is bidirectional, whereby depression increases the risk of diabetes and vice versa (Bruce et al., 2013; Renn et al., 2011). Given the adverse clinical impact, routine screening for depression has been recommended (Egede et al., 2002). However, little is known about the course of depressive symptomatology in this population.

Longitudinal studies reveal that depression in diabetes is often recurrent and persistent (Fisher et al., 2008; Lustman et al., 1997; Nefs et al., 2012; Schmitz et al., 2014). These studies assessed depression at discrete time-points, and defined depression by diagnostic criteria or scoring above a cut-point on depression scales. More gradual changes in depression symptoms over time are, thus, overlooked. Individuals with sub-threshold depression symptoms may be at risk of reduced function and poor quality of life and could benefit from treatment (Schmitz et al., 2014). Identifying longitudinal trajectories of depression symptoms may better reflect the underlying heterogeneity in symptom experience across individuals (Rzewuska et al., 2015).

In addition, investigating associations between temporal changes in depression symptoms and diabetes management may be revealing. While major depression is associated with higher body mass index (BMI), less frequent self-monitoring of blood glucose (SMBG) and worse glycaemic control (Ciechanowski et al., 2003; E. H. B. Lin
et al., 2004; Lustman & Clouse, 2005), the longitudinal relationship between depression severity and these outcomes remains unclear (Fisher et al., 2010; Gonzalez et al., 2007; Gonzalez, Safren, et al., 2008).

The primary aims of this study were to describe trajectories of depression symptoms over a 5-year period in 1,201 participants with Type 2 DM, identify predictors of depression trajectories, and to explore associations between depression trajectories and longitudinal changes in glycaemic control, BMI, and SMBG.

**Subjects and methods**

**Study sample**

The Fremantle Diabetes Study Phase II (FDS2) is an ongoing, longitudinal study of known diabetes, conducted in a postcode-defined, geographic area surrounding the city of Fremantle in the state of Western Australia. Participants (N = 1732) were recruited between 2008 and 2011 through physician and allied health referrals, hospital databases and local advertising (Davis et al., 2013). Of these, 1549 were aged >18 years, had clinically diagnosed Type 2 DM and were eligible for this study. FDS2 was approved by the Human Research Ethics Committees of the South Metropolitan Area Health Service and the University of Western Australia, and participants gave written, informed consent.

**Study procedures**

Comprehensive clinical, biochemical, demographic, depression and psychosocial data were collected at three face-to-face assessments: baseline (Year 0), 2-year follow-up (Year 2), and 4-year follow-up (Year 4). The collected information included all
medications, weekly frequency of SMBG, current smoking status and the number of 
General Practitioner (GP) and outpatient visits. A postal questionnaire in the intervening 
years (Years 1, 3 and 5) provided additional depression data for up to 6 occasions. 
Complete depression data at all 6 time points were available for 195 participants, 294 
had complete data at 5 time points, 225 at 4 time points, 269 at 3 time points, 218 at 2 
time points, and 288 participants had data at one time point only. 

Details of the clinical examination and diabetes diagnosis are reported elsewhere 
(Davis et al., 2013). Briefly, the assessment included fasting serum glucose, HbA_{1c}, 
BMI, and assessment of diabetes complications ascertained using standard criteria 
(Davis et al., 2013).

Depression assessment

Depression symptoms were assessed using the Patient Health Questionnaire-9 
item version (PHQ-9; Kroenke & Spitzer, 2002), a self-report measure validated for use 
in diabetes (E. H. B. Lin et al., 2004; Manea, Gilbody, & McMillan, 2012; van 
Steenbergen-Weijenburg et al., 2010). The PHQ-9 has high sensitivity to detect change 
in depression over time (Löwe et al., 2004) and good agreement with structured 
interview diagnoses (Kroenke & Spitzer, 2002). Total scores range from 0-27 with 
higher scores indicating greater severity. PHQ-9 total scores can be categorized as no 
symptoms (0-4), mild (5-9), moderate (10-14), moderately severe (15-19) and severe 
depression (20+) (Kroenke & Spitzer, 2002). We also considered PHQ-9 cut-off scores 
of 10 and 12, which have been recommended as sensitive and specific cut-points for 
clinical depression in chronic disease and diabetes, respectively (Manea et al., 2012; van
Steenbergen-Weijenburg et al., 2010). Following each assessment, an individuals’ GP was advised if they met criteria for major depression.

The Brief Lifetime Depression Scale (BLDS; Bruce et al., 2013), which has been validated in Type 2 DM (Bruce, Davis, Hunter, et al., 2016), was used to assess for lifetime major depressive disorder (lifetime MDD) at baseline. This measure provides a probable diagnosis of lifetime major depression based on the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria.

**Statistical analysis**

Latent class growth analysis (LCGA) was employed to detect sub-groups of individuals with distinctive patterns of change in depression severity over time, and to estimate the probability of each individual belonging to a particular subgroup (Ram & Grimm, 2009). At the first step, to determine the best single-group representation of change, growth curve models with no growth (intercept only), then with intercept and slope parameters estimated for a linear, quadratic (curvilinear or U-shaped), then logarithmic fit, were estimated (Ram & Grimm, 2009). Model fit was assessed with the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) (Jung & Wickrama, 2008); the Root Mean Square Error of Approximation (RMSEA) (L. Hu & Bentler, 1999); the Standard Root Mean Square Residual (SRMR); and, the Comparative Fit Index (CFI) and Tucker Lewis Index (TLI) (L. Hu & Bentler, 1999).

Missing values analyses indicated that PHQ9 data were not missing at random (NMAR) at baseline, Year 1, 3 or 5 (Little’s MCAR all $p < 0.001$). Missing at random
Depression and Anxiety in T2DM

(MAR), and NMAR pattern-mixture and selection models were generated and model fit compared to determine their likely reliability (B. O. Muthén et al., 2011).

To determine the best fitting number of groups, latent class growth models were built with 2, 3 and 4 groups. The variances of the intercept and slope were allowed to vary within groups (Jung & Wickrama, 2008), and the quadratic term set at zero, as this resulted in the most clinically meaningful groupings with the lowest computational burden (also termed General Growth Mixture Modeling; GGMM). The Vuong-Lo-Mendell-Rubin Likelihood Ratio Test (LRM-LRT) and the Parametric Bootstrap Likelihood Ratio Test (BLRT) were used to determine the improvement in fit when adding a group (Jung & Wickrama, 2008), with significant values indicating improvement in model fit compared with the previous model. High posterior probabilities for each group (≥0.70), and high entropy (near 1.0), were considered to reflect good precision of the model in classifying individuals to each group (Jung & Wickrama, 2008; Nagin & Odgers, 2010).

Identified groups were compared in unadjusted models on baseline demographic, clinical and psychosocial variables using one-way ANOVA for normally distributed data, and non-parametric χ² tests and Mann-Whitney U or Kruskall-Wallis tests for frequency or non-parametric data. Data are presented as proportions, mean±SD or median [inter-quartile range, IQR] for non-normal variables. A binary logistic regression model was used to determine predictors of depression group membership relative to a reference group in adjusted models, and expressed as an odds ratio (OR) and 95% confidence interval (95% CI). Age and gender were entered first, and psychological
variables for which there were significant bivariate differences at baseline were entered subsequently.

Finally, single-growth curve models were generated to represent change in BMI, HbA1c, and frequency of SMBG between Years 0, 2 and 4. Depression group membership was then entered as a predictor of the intercept and slope of these growth curves, to explore whether changes in depression symptoms were associated with change in diabetes management. Lifetime MDD was entered subsequently, to examine whether lifetime depression added utility beyond depression group in explaining diabetes management. Analyses were performed in Mplus Version 7 (L. K. Muthén & Muthén, 1998) and IBM SPSS Version 23. Alpha was 0.05, two-tailed.

Results

Of the 1549 adults with Type 2 DM, 1201 (77.5%) had PHQ-9 data for 2 or more time points and were included in LCGA. Compared to those with inadequate PHQ-9 data, included individuals were less likely to be women (55.2% vs 46.0%, $p=0.002$) or of Aboriginal ethnicity (21.0% vs 2.7%, $p<0.001$), were more likely to be unmarried (35.4% vs 42.9%, $p=0.016$), had shorter diabetes duration (10.0 [3.0-17.6] vs 8.5 [2.3-15.4] years, $p=0.020$), and better glycaemic control (HbA1c: 54 [45-66] vs 51 [44-61] mmol/mol, $p<0.001$) (7.1% [6.3-8.2%] vs 6.8% [6.2-7.6%]). The included participants were also more likely to have received education beyond primary school (88.4% vs 76.2%, $p<0.001$) and to be fluent in English (91.8% vs 80.7%, $p<0.001$). There were no significant differences between included and excluded participants in age (65.3±10.9 vs 65.2±12.4 years, $p=0.93$) or BMI (31.4 ±6.1 vs 31.1±6.6 kg/m², $p=0.47$).
At baseline, 32.7% of the final sample reported mild-to-severe depressive symptoms, with 13.1% scoring above the chronic disease cut-off of 10, and 9.0% scoring above the diabetes cut-off of 12. Criteria for lifetime MDD were met by 34.4% of the sample, and 13.3% were taking antidepressants.

**Depression trajectories**

A quadratic model provided the best single-group representation of the data (Table 7), resulting in the lowest $\chi^2$ (56.48), AIC (26315.83) and parsimony ratio (0.57) statistics. There was no difference between the MAR and NMAR models in the shape of growth curves, number of groups generated, or percentage of individuals in each group, indicating the MAR models as reliable (B. O. Muthén et al., 2011). LCGA revealed the data best fit a 3-group MAR model (see Table 8 and Figure 3). On average, Group 1 (‘no-depression’; 85.2% of the sample) had consistently low depression symptoms over time. Group 2 (‘persistent-depression – low-start’; 7.3%) had depression symptoms below clinical cut-points at baseline that gradually worsened to exceed clinical cut-points over the first 2 years of assessment, plateaued, and then improved to their former level. Group 3 (‘persistent-depression– high-start’; 7.5%) had depression symptoms at baseline that exceeded clinical cut-points, slowly improved over the first 2 years, plateaued but remained above chronic disease cut-points, and then worsened to their former level. Depression symptoms remained elevated over all time-points in both persistent-depression groups. There was no significant difference between the two persistent-depression groups in mean PHQ-9 scores across all time points (high-start vs low-start: 12.4±4.1 vs 11.8±2.9, F (1,136) = 1.0, p=0.31).
Table 7.

**Single growth curve model building for PHQ-9 severity scores (N = 1201)**

<table>
<thead>
<tr>
<th>Model</th>
<th>$\chi^2$</th>
<th>df</th>
<th>$p$</th>
<th>AIC</th>
<th>Parsimony ratio</th>
<th>RMSEA (90% CI)</th>
<th>CFI</th>
<th>TLI</th>
<th>SRMR</th>
<th>Growth parameter estimates</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intercept</td>
<td>Intercept</td>
<td>Slope</td>
<td>Quadratic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept only</td>
<td>81.67</td>
<td>19</td>
<td>&lt;.001</td>
<td>26327.01</td>
<td>0.91</td>
<td>0.05 (0.04-0.06)</td>
<td>.97</td>
<td>.98</td>
<td>.06</td>
<td>4.21†</td>
<td>15.60†</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linear change</td>
<td>68.29</td>
<td>16</td>
<td>&lt;.001</td>
<td>26319.63</td>
<td>0.76</td>
<td>0.05 (0.04-0.07)</td>
<td>.98</td>
<td>.98</td>
<td>.07</td>
<td>4.23†</td>
<td>17.45†</td>
<td>-0.01</td>
<td>0.18†</td>
<td>na</td>
<td>na</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quadratic change*</td>
<td>56.48</td>
<td>12</td>
<td>&lt;.001</td>
<td>26315.83</td>
<td>0.57</td>
<td>0.05 (0.04-0.07)</td>
<td>.98</td>
<td>.98</td>
<td>.06</td>
<td>4.30†</td>
<td>19.64†</td>
<td>-0.18†</td>
<td>1.88†</td>
<td>0.04†</td>
<td>.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Logarithmic change model</td>
<td>63.54</td>
<td>16</td>
<td>&lt;.001</td>
<td>28438.86</td>
<td>0.76</td>
<td>0.04 (0.03-0.06)</td>
<td>.98</td>
<td>.98</td>
<td>.06</td>
<td>4.38†</td>
<td>19.53†</td>
<td>-0.16†</td>
<td>8.69†</td>
<td>na</td>
<td>na</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. AIC = Akaike Information Criterion (lower score = better fit); Parsimony ratio is defined as $df / [.5k(k+1)]$ where $k$ is the number of observed variables; RMSEA = Root Mean Square Error Of Approximation ($<0.06 = $good fit$)$; CFI = Comparative Fit Index; TLI = Tucker Lewis Index ($>0.95 = $good fit$)$; SRMR = Standard Root Mean Square Residual ($<0.05 = $good fit$)$.

*preferred model.

† = $p < 0.05$. 

Depression and Anxiety in T2DM
### Table 8.

**LCGA fit statistics for the PHQ9 latent class quadratic growth model (N = 1201)**

<table>
<thead>
<tr>
<th></th>
<th>1-Class</th>
<th>2-Class</th>
<th>3-Class*</th>
<th>4-Class</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sample size</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 1</td>
<td>1201 (100%)</td>
<td>1066 (88.76%)</td>
<td>1023 (85.18%)</td>
<td>944 (78.60%)</td>
</tr>
<tr>
<td>N = 2</td>
<td>135 (11.24%)</td>
<td>90 (7.49%)</td>
<td>134 (11.16%)</td>
<td></td>
</tr>
<tr>
<td>N = 3</td>
<td>88 (7.33%)</td>
<td>77 (6.41%)</td>
<td>46 (3.83%)</td>
<td></td>
</tr>
<tr>
<td>N = 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fit Statistics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># of Parameters</td>
<td>12</td>
<td>16</td>
<td>20</td>
<td>24</td>
</tr>
<tr>
<td>AIC</td>
<td>26317.16</td>
<td>25903.55</td>
<td>25680.87</td>
<td>25532.25</td>
</tr>
<tr>
<td>BIC</td>
<td>26378.25</td>
<td>25985.01</td>
<td>25782.69</td>
<td>25654.43</td>
</tr>
<tr>
<td>ABIC</td>
<td>26340.13</td>
<td>25934.19</td>
<td>25719.16</td>
<td>25578.20</td>
</tr>
<tr>
<td>Entropy</td>
<td></td>
<td>0.922</td>
<td>0.924</td>
<td>0.907</td>
</tr>
<tr>
<td>Log likelihood</td>
<td>-13146.58</td>
<td>-12935.78</td>
<td>-12820.43</td>
<td>-12742.13</td>
</tr>
<tr>
<td>LRM-LRT p value</td>
<td>na</td>
<td>0.020</td>
<td>0.002</td>
<td>0.115</td>
</tr>
<tr>
<td>BLRT p value</td>
<td>na</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

**Note.** AIC = Akaike Information Criterion (lower score = better fit); BIC = Bayesian Information Criterion (lower score = better fit); ABIC = adjusted Bayesian Information Criterion (lower score = better fit); LRM-LRT = Vuong-Lo-Mendell-Rubin Likelihood Ratio Test (significant p value = improvement in model fit from previous number of classes); BLRT = Bootstrap Likelihood Ratio Test (significant p value = improvement in model fit). * = preferred model.
Figure 3. Estimated mean PHQ-9 total scores for the 3-group quadratic LCGA trajectories over 5 years, including recommended chronic disease (PHQ-9 >10) and diabetes (PHQ-9 >12) cut-offs for clinically significant depression.
Baseline characteristics associated with depression groups

Baseline characteristics of the three groups are presented in Table 9. Compared with both persistent-depression groups, individuals in Group 1 were older at diabetes diagnosis, had lower BMI, and reported less lifetime MDD. Compared with Group 1, Group 3 were more likely to smoke, had worse glycemic control, more macrovascular complications and attended more GP visits, and Group 2 attended more outpatient visits in the previous year. Whilst individuals in Group 2 were more likely than Group 1 to have macrovascular complications (47% vs 37%) and higher HbA1c (54 vs 50 mmol/mol; 7.1 vs 6.7%), these were not statistically significant. Group 3 were younger and more likely to smoke than Group 2.

Fewer antidepressants were prescribed to Group 1 participants than both Groups 2 and 3 (Table 9), and most were taken by Group 3. Antidepressant use remained higher at all time-points for Group 2 (Year 2: 27.4%; Year 4: 35.4%) and Group 3 (Year 2: 35.4%; Year 4: 35.1%) relative to Group 1 (p<0.001), with no significant differences between Groups 2 and 3 over time (p>0.05).
Table 9.

**Baseline characteristics among 1,201 people with Type 2 DM, stratified by depression group. Data are presented as proportions, means±standard deviations, or medians [interquartile range]**

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Group 1: “No depression” (85.2%) n = 1023</th>
<th>Group 2: “Persistent depression – low-start” (7.3%) n = 88</th>
<th>Group 3: “Persistent depression – high-start” (7.5%) n = 90</th>
<th>Pairwise comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>66.0±10.6</td>
<td>63.4±11.8</td>
<td>58.8±11.7</td>
<td>b(^\dagger)c(^\dagger)</td>
</tr>
<tr>
<td>Age at diabetes diagnosis</td>
<td>56.2±11.3</td>
<td>52.3±12.3</td>
<td>48.7±10.7</td>
<td>a(^\dagger)b(^\dagger)</td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>8 [2-15.3]</td>
<td>10 [3.3-15.9]</td>
<td>10 [4-16.3]</td>
<td></td>
</tr>
<tr>
<td>Gender, % women</td>
<td>44.1</td>
<td>52.3</td>
<td>61.1</td>
<td>b(^\dagger)</td>
</tr>
<tr>
<td>Ethnicity, % Anglo-Celt</td>
<td>60.0</td>
<td>56.8</td>
<td>45.6</td>
<td>b(^\dagger)c(^\dagger)</td>
</tr>
<tr>
<td>English fluency, % non-fluent</td>
<td>7.4</td>
<td>10.2</td>
<td>14.4</td>
<td>b(^\dagger)</td>
</tr>
<tr>
<td>Education, % primary or less</td>
<td>9.9</td>
<td>13.6</td>
<td>13.6</td>
<td></td>
</tr>
<tr>
<td>Marital status, % single</td>
<td>34.2</td>
<td>37.5</td>
<td>47.1</td>
<td>b(^\dagger)</td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>30.9±5.8</td>
<td>34.7±7.7</td>
<td>33.5±6.4</td>
<td>a(^\dagger)b(^\dagger)</td>
</tr>
<tr>
<td>HbA(_{1c}), mmol/mol (%)</td>
<td>50 [44-58]</td>
<td>54 [45-62]</td>
<td>54 [44-69]</td>
<td>b(^\dagger)</td>
</tr>
<tr>
<td>(6.7 [6.2-7.5])</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting serum glucose</td>
<td>7.1 [6.2-8.5]</td>
<td>7.5 [6.4-9.2]</td>
<td>7.8 [6.1-11.0]</td>
<td>b(^\dagger)</td>
</tr>
<tr>
<td>Diabetes treatment, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet/exercise</td>
<td>27.4</td>
<td>11.4</td>
<td>17.8</td>
<td>a(^\dagger)b(^\dagger)</td>
</tr>
<tr>
<td>Oral glucose lowering medications (OGLMs)</td>
<td>52.6</td>
<td>62.5</td>
<td>48.9</td>
<td>c(^\dagger)</td>
</tr>
<tr>
<td>Insulin only</td>
<td>3.8</td>
<td>4.5</td>
<td>8.9</td>
<td>b(^\dagger)</td>
</tr>
<tr>
<td>Insulin + OGLMs</td>
<td>16.2</td>
<td>21.6</td>
<td>24.4</td>
<td>b(^\dagger)</td>
</tr>
</tbody>
</table>
### Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group 1: “No depression” 85.2% (n = 1023)</th>
<th>Group 2: “Persistent depression – low-start” 7.3% (n = 88)</th>
<th>Group 3: “Persistent depression – high-start” 7.5% (n = 90)</th>
<th>Pairwise comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of medical visits in past year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Practitioner</td>
<td>3.0 [2-4]</td>
<td>4.0 [2-10]</td>
<td>4.0 [2-12]</td>
<td>b†</td>
</tr>
<tr>
<td>Diabetes outpatient clinic visit</td>
<td>0.0 [0-0]</td>
<td>0.0 [0-2]</td>
<td>0.0 [0-1]</td>
<td>a^b†</td>
</tr>
<tr>
<td>Diabetes-related outpatient clinic visit</td>
<td>0.0 [0-0]</td>
<td>1.0 [0-2]</td>
<td>0.0 [0-1]</td>
<td>a†</td>
</tr>
<tr>
<td>Self-management and health outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMBG number of times per week</td>
<td>5.0 [2.0-10.0]</td>
<td>6.5 [1.0-14.0]</td>
<td>5.0 [0-14.0]</td>
<td></td>
</tr>
<tr>
<td>SMBG, % yes</td>
<td>86.6</td>
<td>86.0</td>
<td>78.3</td>
<td>c†</td>
</tr>
<tr>
<td>Self and/or other monitoring of blood glucose, % yes</td>
<td>87.7</td>
<td>90.7</td>
<td>79.5</td>
<td>b^c†</td>
</tr>
<tr>
<td>Smoking status, % current</td>
<td>7.4</td>
<td>4.5</td>
<td>16.7</td>
<td>b^c†</td>
</tr>
<tr>
<td>Macrophage complications, % yes</td>
<td>37.0</td>
<td>46.6</td>
<td>51.1</td>
<td>b†</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy, % yes</td>
<td>59.5</td>
<td>55.7</td>
<td>54.4</td>
<td></td>
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</tbody>
</table>

### Psychological characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group 1: “No depression” 85.2% (n = 1023)</th>
<th>Group 2: “Persistent depression – low-start” 7.3% (n = 88)</th>
<th>Group 3: “Persistent depression – high-start” 7.5% (n = 90)</th>
<th>Pairwise comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHQ-9 total score</td>
<td>2.0 [0-4.0]</td>
<td>9.0 [5.8-11.0]</td>
<td>16.0 [13.0-20.0]</td>
<td>a^b^c†</td>
</tr>
<tr>
<td>Antidepressant use, % current</td>
<td>9.3</td>
<td>31.0</td>
<td>42.2</td>
<td>a^b†</td>
</tr>
<tr>
<td>Lifetime major depression, % yes</td>
<td>27.9</td>
<td>64.8</td>
<td>78.9</td>
<td>a^b^c†</td>
</tr>
</tbody>
</table>

**Note.** Only significant pairwise comparisons are presented; HbA1c = glycated hemoglobin; SMBG = self-monitoring of blood glucose; lifetime MDD = Lifetime Major Depressive Disorder.

a = difference between Group 1 and Group 2.

b = difference between Group 1 and Group 3

c = difference between Group 3 and Group 2.

† = significant at \( p < .05 \), ‡ = significant at \( p < .001 \).
Given the similarity in the pattern of persistent and apparently cyclical depression symptoms in both persistent-depression groups, and the similarities in baseline characteristics, we combined Groups 2 and 3 and compared them with Group 1 to explore the role of lifetime MDD and demographic variables. Age and gender were entered into the first step as known correlates of depression, with younger age (OR 0.96, 95% CI 0.95, 0.98, per year) and female sex (OR 1.61, 95% CI 1.14, 2.28) significantly associated with membership of the combined persistent-depression groups. Lifetime MDD was associated with a six-fold increase in the odds of being in the persistent-depression groups (OR 6.39, 95% CI 4.31, 9.49) after age- and gender-adjustment.

**Associations between depression group and diabetes management**

Single growth curve models were generated for BMI, HbA1c and SMBG (presented in Table B1). To determine whether the identified depression groups were associated with either baseline (intercept), or changes in (slope) diabetes management, group membership was entered as a predictor of these curves. Relative to Group 1, persistent-depression was associated with higher BMI (intercept term; model 1a, Table 10), but not with baseline HbA1c or SMBG (models 2a, 3a), or with the slope (change) of any variable. At the second step, entering lifetime MDD into the model did not improve prediction of the intercept or slope of any variable (Table 10: models 1b, 2b, 3b).
Table 10.

*Individual models of BMI, HbA1c and SMBG as longitudinal correlates of persistent-depression group and lifetime MDD*

<table>
<thead>
<tr>
<th>Model</th>
<th>Diabetes management variable</th>
<th>Predictor/associate*</th>
<th>$\chi^2$</th>
<th>df</th>
<th>$p$</th>
<th>AIC (90% CI)</th>
<th>RMSEA</th>
<th>CFI</th>
<th>TLI</th>
<th>SRMR</th>
<th>Growth parameter estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Intercept on predictor Mean</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Slope on predictor Mean</td>
</tr>
<tr>
<td>1a</td>
<td>BMI</td>
<td>Persistent depression</td>
<td>5.15</td>
<td>6</td>
<td>0.52</td>
<td>15496.63 (0-0.04)</td>
<td>1.00</td>
<td>1.00</td>
<td>0.00</td>
<td>2.23†</td>
<td>-0.08</td>
</tr>
<tr>
<td>1b</td>
<td>BMI</td>
<td>Persistent depression</td>
<td>5.63</td>
<td>7</td>
<td>0.58</td>
<td>14910.58 (0-0.03)</td>
<td>1.00</td>
<td>1.00</td>
<td>0.00</td>
<td>1.92†</td>
<td>-0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lifetime MDD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2a</td>
<td>HbA1c</td>
<td>Persistent depression</td>
<td>4.60</td>
<td>6</td>
<td>0.60</td>
<td>9342.69 (0-0.03)</td>
<td>1.00</td>
<td>1.00</td>
<td>0.01</td>
<td>0.56</td>
<td>-0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lifetime MDD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2b</td>
<td>HbA1c</td>
<td>Persistent depression</td>
<td>4.85</td>
<td>7</td>
<td>0.68</td>
<td>8866.12 (0-0.03)</td>
<td>1.00</td>
<td>1.01</td>
<td>0.01</td>
<td>0.21</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lifetime MDD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3a</td>
<td>SMBG</td>
<td>Persistent depression</td>
<td>13.18</td>
<td>6</td>
<td>0.04</td>
<td>21357.36 (0.01-0.06)</td>
<td>0.99</td>
<td>0.97</td>
<td>0.01</td>
<td>1.25</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lifetime MDD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3b</td>
<td>SMBG</td>
<td>Persistent depression</td>
<td>13.86</td>
<td>7</td>
<td>0.05</td>
<td>20506.83 (0-0.05)</td>
<td>0.99</td>
<td>0.97</td>
<td>0.01</td>
<td>1.49</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lifetime MDD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.41</td>
</tr>
</tbody>
</table>

*Note.* AIC = Akaike Information Criterion (lower score = better fit); RMSEA = Root Mean Square Error Of Approximation (<0.06 = good fit); CFI = Comparative Fit Index; TLI = Tucker Lewis Index (>0.95 = good fit); SRMR = Standard Root Mean Square Residual (<0.05 = good fit); BMI = body mass index; Persistent depression = depression trajectory group (0 = no depression, 1 = persistent depression); BMI = body mass index; SMBG = self-monitoring blood glucose; Lifetime MDD = lifetime major depressive disorder. * covariates accounted for in all models were age, disease duration, gender, and marital status. † = $p < .05$. 
Discussion

This is the first study to use LCGA to examine the natural history of depression symptomatology in Type 2 DM. Three clinical groups were identified in a large, representative, community-based sample. The largest group (Group 1) had consistently absent or low depression symptoms. The other two groups (2 and 3) displayed a pattern of mild to moderate depression symptoms that persisted over the 5-year period, and cycled above and below clinical cut-points for major depression but never entirely remitted. Previous studies have estimated that clinically-elevated depression symptoms may persist in up to 9% of individuals with type 2 DM over 18 months (Fisher et al., 2008), and the present findings indicate that this can continue for considerably longer. The cyclical nature of depression severity suggests that more individuals with type 2 DM experience elevated depression symptoms than indicated by prevalence estimates based on clinical cut-offs at a single time-point.

Both persistent-depression groups demonstrated similar patterns of cyclical depression symptoms. Although the high-start group reached higher ‘peaks’ in the cycle, there appeared to be no difference in total exposure to depression severity. Between-group comparisons revealed few clinical differences. Both were similar in baseline BMI, HbA$_1c$, chronic complications, and in the prevalence of lifetime MDD, and both were more likely to be female, younger, to access healthcare services, to be prescribed antidepressants, and to have persistently higher BMI (de Groot et al., 2001; Egede et al., 2002; Fisher et al., 2008). Whilst the high-start persistent-depression group was younger, more likely to smoke and was less adherent to medications and SMBG than the low-start
persistent-depression group, this could be explained by differences in depression severity at baseline (E. H. B. Lin et al., 2004; Whitworth et al., 2016). We believe that these two groups represent similar patterns of underlying depression symptom change, with little difference in clinical outcome. One explanation is that individuals were captured at different phases of a similar cycle, based on the arbitrary timing of study entry. However, it is also possible that these groups may be clinically distinct and display different patterns of depression symptom change with ongoing assessment. Longer-term follow up is needed to clarify this, and to determine whether differential depression management is warranted for those with more severe depression symptoms at baseline.

One prior study has investigated depression trajectories in Type 2 DM (Schmitz et al., 2013). Schmitz and colleagues (Schmitz et al., 2013) identified four groups based on patterns of change in categorical depression diagnoses over 3-years: a majority non-depressed group, a group with worsening major depression, a group with increasing prevalence of major and minor depression, and an improved depression group. The present findings are consistent with this study but suggest that longer follow-up may have led to different conclusions. An extension of Schmitz and colleagues’ findings would help to determine whether a cyclical pattern is replicated long-term, as has been shown by fluctuating depression diagnoses over 10 years in the general population (Kennedy et al., 2004).

A key finding of the present study is that lifetime MDD was the strongest risk factor for persistent depression symptoms, increasing the risk six-fold. In cross-sectional
studies based on the baseline FDS2 data set, we previously reported that lifetime MDD was associated with current depression (Bruce, Davis, Hunter, et al., 2016) and depression symptom severity (Whitworth et al., 2016). The present study extends these findings longitudinally, emphasizing the importance of lifetime MDD as a risk factor for persistent depression in type 2 DM. There were no significant associations between change in depression symptoms and change in either HbA1c or SMBG, consistent with previous report (Fisher et al., 2010). Given diabetes requires daily management for optimal control, changes in diabetes management may be more proximally predicted by an individual’s current level of distress (Fisher et al., 2010).

These data have important clinical implications. Current recommendations are that stepped-care depression management is offered based on screening positively at a given time-point for either a depression diagnosis or scoring above a clinical cut-point. The results of this study indicate that this approach is likely to miss individuals with subthreshold depression symptoms who may benefit from preventive treatment (Schmitz et al., 2014). In the FDS2, participants’ GPs were notified if they had major depression but, while antidepressant use was highest in the persistent-depression groups, depression symptoms continued to recur. The results suggest that regular monitoring of depression symptoms is warranted, especially for those with lifetime MDD or with sub-threshold depression, in order to identify at-risk individuals in need of more intensive depression management. Screening for lifetime MDD with an instrument such as the BLDS at diabetes diagnosis may provide an opportunity for targeted and pro-active monitoring of depression.
The strengths of the present study include the assessment of the course of depression symptoms across 6 time-points, using a longitudinal modeling technique that allows naturally occurring trajectories to arise from the data (Nagin & Odgers, 2010). Benefits of LCGA over traditional methods include the ability empirically to test how well the models fit the data, rather than subjectively deciding on the number of hypothesized groups \textit{a priori} (Nagin & Odgers, 2010). This reduces the chance of bias when deciding on the best-fitting number of groups, and provides the most parsimonious interpretation (Nagin & Odgers, 2010). LCGA also incorporated intermittent PHQ-9 data into the analyses, rather than excluding those with incomplete data and potentially biasing estimates (B. O. Muthén et al., 2011). A potential limitation is that more clinical groups may exist in the data, but are not included in the final model as they do not substantively improve model fit, or contain too few individuals (Jung & Wickrama, 2008).

Limitations of this study include self-report measures that may result in over-diagnosis compared with gold-standard clinical interviews, and the potential overlap between ratings of lifetime and current depression at baseline. However, the PHQ-9 has high sensitivity for symptomatic and diagnostic change across repeated assessments (Löwe et al., 2004) and the BLDS has high diagnostic concordance with clinical interview (Bruce et al., 2013). Finally, symptoms of anxiety and diabetes distress are highly comorbid with depression and may influence the experience of depression symptoms over time (Fisher et al., 2008). This overlap warrants further investigation.
In conclusion, the present study demonstrates that a sub-set of individuals with diabetes experience mild to high levels of depression symptoms that persist. Regular screening for depression severity, in addition to assessment of lifetime depression and psychosocial functioning, may better identify individuals at risk of a later relapse or progression in symptoms and enable more targeted intervention.
Chapter 5: Anxiety in Type 2 Diabetes: Risk Factors and Outcomes of 4-Year Anxiety Symptom Trajectories Using Latent Growth Mixture Modeling.

This chapter has been prepared as a manuscript for submission to *Diabetes Care*: Whitworth, S.R., Bruce, D.G., Starkstein, S.E., Davis, W.A., Davis, T.M.E., Skinner, T.C., & Bucks, R.S. Anxiety in type 2 diabetes: risk factors and outcomes of 4-year anxiety symptom trajectories using latent growth mixture modeling. It is presented below, as prepared for submission, but formatted for consistency with the rest of the thesis.

**Preface**

Study 2 (Chapter 4) examined the course of continuous depression symptom severity in T2DM. This study revealed two groups of particular clinical interest, as members of both groups displayed a pattern of cycling and persistent depression symptoms over 5 years. This Chapter (Study 3) extended these findings to consider the developmental course of generalized anxiety disorder symptoms in T2DM. Given the high comorbidity between depression and anxiety reported in the literature, and demonstrated in Chapter 1, overlap between the persistent-depression groups from Study 2 and the anxiety groups identified in Study 3 was also examined.

There was no significant change in BMI, HbA1c, or SMBG over time in Study 2, and thus depression group membership was not found significantly to predict longitudinal diabetes management and control. Study 3 thus employed a different statistical method, Latent Growth Mixture Modeling (LGMM), to instead examine
predictors of anxiety groups, and whether anxiety group membership then predicted long-term health outcomes.
**Abstract**

**Background:** Generalized anxiety disorder may be an important comorbidity in type 2 diabetes. There is a paucity of research investigating the course of anxiety in this population. This study aimed to describe 4-year trajectories of anxiety symptoms and to identify determinants and outcomes in a community-based cohort with type 2 diabetes.

**Methods:** Participants of the Fremantle Diabetes Study-Phase II with type 2 diabetes (N=1091) completed the Generalized Anxiety Disorder Scale at baseline and biennially for 4 years. The baseline and year 4 assessments included a range of psychological, biomedical and self-management measures. Latent growth mixture modeling was used to identify trajectories of anxiety symptom severity, and regression models determined predictors of trajectory membership and associated outcomes.

**Results:** Two distinct groups of anxiety symptoms were identified: continuously low-to-no anxiety symptoms (87.4%), and high anxiety symptoms which began to improve but remained consistently elevated (elevated anxiety; 12.6%). Higher HbA$_1$c and BMI, more macrovascular complications, and a history of generalized anxiety and major depression, significantly increased the risk of elevated-anxiety. Elevated-anxiety did not predict change in health-related outcomes over time. Elevated-anxiety and depression symptoms were highly comorbid, and these individuals displayed the most chronic pattern of anxiety.

**Conclusions:** A sub-group of individuals with type 2 diabetes are at risk of elevated anxiety symptoms which do not remit. Routine monitoring of the severity of anxiety and depression symptoms in this population, especially for those younger in age, overweight
and of poorer health, may be required to enable earlier and more intensive mood management.
Depression and Anxiety in T2DM

Introduction

Depression is widely recognized to impact substantially on the management and sequelae of type 2 diabetes (de Groot et al., 2001; Gonzalez et al., 2007). Anxiety disorders, of which generalized anxiety disorder (GAD) is the most common, have received significantly less attention. GAD frequently presents as persistent worry about a number of life areas, in addition to physiological and behavioural symptoms (Smith et al., 2013). This disorder is estimated to affect up to 14% of individuals with type 2 diabetes, with 25-40% experiencing increased anxiety symptoms (Grigsby et al., 2002; Hermanns, Kulzer, Krichbaum, Kubiak, & Haak, 2005). In cross-sectional studies, GAD has been associated with an increased risk of diabetes complications (Collins et al., 2009), worse glycemic control (Anderson et al., 2002; Balhara & Sagar, 2011), greater neuropathic pain (Gore et al., 2005; Jain, Jain, Raison, & Maletic, 2011), obesity (Balhara & Sagar, 2011), and lower quality of life (Paschalides et al., 2004). However, the long-term development and impact of anxiety symptoms in type 2 diabetes, and implications for intervention, remain unclear.

General population studies indicate a GAD diagnosis can be chronic, though less stable than depression (Schoevers et al., 2005; Wittchen, Lieb, Pfister, & Schuster, 2000), with symptoms improving for a sub-set of individuals (Ramsawh et al., 2009). In type 2 diabetes, one longitudinal study found that the proportion of individuals meeting criteria for a GAD diagnosis declined over 18-months (Fisher et al., 2008). However, it is likely that these studies did not capture the broader spectrum of anxiety symptoms as they only assessed clinical diagnoses. Furthermore, research lacks consensus concerning
the strength and direction of the temporal relationships between anxiety, glycemic control and diabetes complications (Anderson et al., 2002; Hermanns et al., 2005; Smith et al., 2013). Given that subthreshold anxiety symptoms are an important precursor to GAD (Smith et al., 2013), examining the longitudinal associations between anxiety symptoms and health-related outcomes may be of substantial clinical relevance.

We recently identified, in a large cohort of individuals with type 2 diabetes followed for 5 years, two groups of individuals who experienced persistently elevated depression symptoms over time (Whitworth et al., 2017). These symptoms often cycled below cut-points for clinically-significant depression but never fully remitted, and were associated with reduced psychological and health-related function. Applying this approach to trajectories of anxiety symptoms may be similarly revealing. Further, given the known overlap between anxiety and depression in diabetes (Collins et al., 2009; Deschênes et al., 2015), and the greater likelihood of recurrence of both disorders when they present together (Merikangas et al., 2003), determining the natural history of anxiety symptoms should also improve our understanding of this important comorbidity.

The primary aim of the present study was to identify trajectories of anxiety symptoms over a 4-year period in 1,091 individuals with type 2 diabetes, to identify predictors of these trajectories, and to explore whether anxiety trajectories are determinants of glycaemic control and chronic complications. A secondary aim was to examine the degree and impact of the overlap between anxiety symptom trajectories and our previously published persistent-depression groups.
Research Design and Methods

Study sample

The Fremantle Diabetes Study Phase II (FDS2) is a longitudinal observational study of known diabetes, conducted in a postcode-defined geographical area surrounding the city of Fremantle in the state of Western Australia (Davis et al., 2013). Details of FDS2 recruitment procedures have been published elsewhere (Davis et al., 2000, 2013). Briefly, 1,732 participants were recruited to the baseline arm of FDS2 between 2008-2011 through physician and allied health referrals, hospital databases, local advertising and word-of-mouth (Davis et al., 2013). Of these, 1549 were > 18 years with clinically diagnosed type 2 diabetes and included in this study. The Human Research Ethics Committee of the South Metropolitan Area Health Service and the University of Western Australia approved the study, and all participants gave written, informed consent.

Study procedures

Each participant underwent a comprehensive clinical examination, in addition to collection of demographic and mood data, during a face-to-face assessment at study entry and at subsequent two-year intervals. Anxiety data were potentially available for a maximum of 3 occasions (Year 0, Year 2, and Year 4). Complete data at all 3 time points were available for 801 participants, 290 had complete data at two time points, 380 at one time point only, and 78 participants had missing data at all 3 assessments.

Full details of FDS2 assessments are reported elsewhere (Davis et al., 2013), but these included demographic characteristics, diabetes duration, current blood glucose-
lowering treatment, frequency of self-monitoring of blood glucose (SMBG), smoking status and antidepressant use, as well as the number of primary care and hospital clinic visits in the past year. Body mass index was measured and macrovascular and microvascular complications were ascertained using standard criteria (Davis et al., 2013). Fasting biochemical tests including fasting serum glucose and HbA1c were also carried out.

**Mood assessment**

Anxiety symptom severity was assessed using the Generalized Anxiety Disorder Scale (GADS; Starkstein et al., 2014), an assessment that has been validated in the FDS2 for use in type 2 diabetes (Starkstein et al., 2014). The GADS demonstrated good test-retest reliability (Starkstein et al., 2014), and provides a probable diagnosis of GAD based on the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria. The GADS items were rated as “not at all present”, “present several days”, “present more than half of the days”, and “present nearly every day”, with an item scored positively if endorsed as “more than half the days” or above. Probable GAD was classified if individuals endorsed experiencing excessive worry and difficulty controlling their worries, for more than half the days over the past 6 months, in addition to 3 or more positive anxiety symptoms. Total scores range from 0-24 with higher scores indicating more severe anxiety. To determine the optimal cut-point for detecting clinically significant anxiety, the GADS was further validated in a stratified sample of 57 individuals from the FDS2 against the SCID-RV-Anxiety Disorders Module. ROC curve analysis was performed, and based on the area under the curve and sensitivity and
specificity values, a cut-off of 15 was chosen (Hanley & McNeil, 1982). This cut-off resulted in the highest sensitivity (83.3%) and specificity (92.2%), and an area under the curve of 0.93 indicating that 93% of individuals who met GAD criteria on the SCID-RV also had a higher score on the GADS.

The Generalized Anxiety Disorder – Lifetime Scale (GAD-LT) was used to assess for lifetime GAD. This instrument was designed for the FDS2 to map on to the GADS, with the time criterion set to one month to reflect DSM-IV lifetime criteria. The GAD-LT provides a probable diagnosis of lifetime generalized anxiety based on DSM-IV criteria, and has been validated for use in type 2 diabetes (Whitworth et al., 2016).

The severity of depression symptoms was assessed using the Patient Health Questionnaire-9 item version (PHQ-9; Kroenke & Spitzer, 2002), a self-report measure widely validated for use in diabetes (van Steenbergen-Weijenburg et al., 2010). PHQ-9 total scores range from 0-27 with higher scores indicating more severe symptoms. This measure was administered annually in the same sample, and total PHQ-9 scores at each assessment were used to identify trajectories of depression symptoms in our previously published study (Whitworth et al., 2017). Finally, the Brief Lifetime Depression Scale (BLDS; Bruce et al., 2013), an assessment designed for use in type 2 diabetes and mapping onto DSM-IV criteria (Bruce et al., 2013), assessed for lifetime prevalence of major depressive disorder (lifetime major depression) at baseline.

**Statistical analysis**

**Anxiety trajectories.** Latent growth mixture modeling (LGMM) was used to identify sub-groups of people who displayed a similar trajectory of anxiety symptom...
Depression and Anxiety in T2DM

severity over time, based on changes in GADS total scores. LGMM examines whether there exist sub-groups of individuals within the sample who share distinctive patterns of symptom change, and estimates the probability of each individual belonging to a particular group (Ram & Grimm, 2009).

To determine the best single-group representation of change, growth curve models with no growth (intercept only), and with intercept and slope parameters, were estimated for a linear and logarithmic fit (Ram & Grimm, 2009). The following methods were used to assess model fit: the Bayesian Information Criterion (BIC) and Akaike Information Criterion (AIC) (Hoyle, 2012); the Root Mean Square Error of Approximation (RMSEA); the Standard Root Mean Square Residual (SRMR); and the Tucker Lewis Index (TLI) and Comparative Fit Index (CFI) (Hoyle, 2012). Missing values analyses revealed GADS data were missing completely at random at Year 0 and Year 4 (Little’s MCAR $p>0.05$) and missing at random at Year 2 (Little’s MCAR $\chi^2(205)=289.38, p<0.001$). There was less than 5% missingness at all assessments, so expectation maximization was employed to impute missing values.

Next, LGMM was performed with 1-3 classes to determine the best fitting number of groups, with variances of the intercept and slope allowed to vary (Jung & Wickrama, 2008). The Vuong-Lo-Mendell-Rubin Likelihood Ratio Test (LRM-LRT) and Parametric Bootstrap Likelihood Ratio Test (BLRT) were used to determine improvement in fit when including an extra group (Lo et al., 2001). High posterior probabilities for each class and high entropy were considered to reflect good model precision (Jung & Wickrama, 2008; Nagin, 2005).
Predictors of anxiety group membership were examined using unadjusted bivariate regression models. To delineate the contribution of lifetime generalized anxiety and major depression to group membership, an adjusted logistic regression model was performed with significant bivariate demographic characteristics entered into the first step, followed by lifetime anxiety, then lifetime depression. Anxiety group membership was then used to predict clinical outcomes at Year 4 using bivariate regression models, performed with and without controlling for these variables at baseline.

Finally, \( \chi^2 \) tests, one-way ANOVA, or Kruskall-Wallis tests for non-parametric data, were used to examine the degree of overlap between identified anxiety groups, and those with persistent-depression symptoms as described previously (Whitworth et al., in press). Between-group differences for those with and without overlapping anxiety and depression symptom trajectories in clinical and psychological variables, were explored at baseline. Differences in GADS total scores were compared at Year 0, 2 and 4. Analyses were performed using Mplus Version 7 and IBM SPSS Statistics Version 23. Alpha was 0.05, two-tailed. Data are presented as proportions, mean±SD, or median [inter-quartile range, IQR] for non-normal variables, and Bonferroni correction was applied to adjust for multiple comparisons.

**Results**

Of the 1,549 adults with type 2 diabetes, 1,091 had GADS data for 2 or more time points and were included in LGMM. Compared to included participants, those with inadequate GADS data were older (64.8±10.8 vs 66.4±12.2 years, \( p = 0.02 \)), had longer diabetes duration (8.0 [2.0-15.1] vs 10.6 [4.0-18.0] years, \( p<0.001 \)), higher HbA1c (6.8%
Depression and Anxiety in T2DM

[6.2%-7.5%] vs 7.0% [6.3%-8.1%]) (51 [44-58] vs 53 [45-65] mmol/mol, \(p<0.001\)), and were less likely to have received secondary education (90.5% vs 77.0%, \(p<0.001\)) or to be of Anglo-Celt ethnicity (58.8% vs 40.4%, \(p<0.001\)). Excluded participants were more likely to be female (45.4% vs 54.4%, \(p<0.001\)) and to be unmarried (12.3% vs 44.1%, \(p<0.001\)). There were no significant between-group differences in BMI (31.4±5.9 vs 31.8±6.8, \(p=0.30\)).

At baseline, 6.2% of the final sample met DSM-IV criteria for current GAD and 7.1% endorsed symptoms of anxiety above the clinical cut-point of 15. The mean GADS score for the overall sample was 5.6±5.2. DSM-IV criteria for lifetime generalized anxiety were met by 26.7% and 35.9% for lifetime major depression, and 13.1% were taking antidepressants.

**Anxiety trajectories**

A linear model emerged as the best fitting single growth model for GADS data, Table C1). At the next step, LGMM revealed the GADS data best fit a linear 2-group model (see Figure 4 and Table 11). Group 1 (‘no anxiety’; 87.4%), the majority of the sample, had low-to-no anxiety symptoms over time (GADS total score at baseline = 4.1±3.2). Group 2 (‘elevated-anxiety’; 12.6%) displayed a pattern of anxiety symptoms that fell above the clinical cut-point at baseline (GADS total score = 16.2±3.7), gradually improved to below this cut-off over time, but remained elevated. Of clinical relevance, anxiety symptoms were significantly higher in this group at all assessments relative to the no-anxiety group (Year 0: \(F(1,1075)=1595.34, p<0.001\); Year 2: \(F(1,1051)=338.17, p<0.001\); Year 4: \(F(1,851)=106.71, p<0.001\).
Figure 4. Mean estimated anxiety scores (GADS total scores) for 2-class LGMM over 4 years, including clinical cut-off (GADS ≥ 15).
Table 11.

*LGMM fit statistics for GADS unconditional latent linear growth model (N = 1091)*

<table>
<thead>
<tr>
<th>Sample size</th>
<th>1-Class LGMM</th>
<th>2-Class LGMM&lt;sup&gt;1&lt;/sup&gt;</th>
<th>3-Class LGMM</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 1</td>
<td>1091 (100%)</td>
<td>954 (87.44%)</td>
<td>914 (83.78%)</td>
</tr>
<tr>
<td>N = 2</td>
<td>-</td>
<td>137 (12.56%)</td>
<td>91 (8.34%)</td>
</tr>
<tr>
<td>N = 3</td>
<td>-</td>
<td>-</td>
<td>86 (7.88%)</td>
</tr>
</tbody>
</table>

**Fit Statistics**

<table>
<thead>
<tr>
<th># of Parameters</th>
<th>1-Class LGMM</th>
<th>2-Class LGMM&lt;sup&gt;1&lt;/sup&gt;</th>
<th>3-Class LGMM</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIC</td>
<td>17150.95</td>
<td>16919.72</td>
<td>16784.48</td>
</tr>
<tr>
<td>BIC</td>
<td>17190.91</td>
<td>16974.66</td>
<td>16854.41</td>
</tr>
<tr>
<td>ABIC</td>
<td>17165.50</td>
<td>16939.73</td>
<td>16809.94</td>
</tr>
<tr>
<td>Entropy</td>
<td>na</td>
<td>0.879</td>
<td>0.871</td>
</tr>
<tr>
<td>Log likelihood</td>
<td>-8567.48</td>
<td>-8448.86</td>
<td>-8378.24</td>
</tr>
<tr>
<td>LRM-LRT p-value</td>
<td>na</td>
<td>&lt;0.001</td>
<td>0.194</td>
</tr>
<tr>
<td>BLRT p-value</td>
<td>na</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Note.* AIC = Akaike Information Criterion (lower score = better fit); BIC = Bayesian Information Criterion (lower score = better fit); ABIC = adjusted Bayesian Information Criterion (lower score = better fit); LRM-LRT = Vuong-Lo-Mendell-Rubin Likelihood Ratio Test (significant p value = improvement in model fit); BLRT = Bootstrap Likelihood Ratio Test (significant p value = improvement in model fit).<sup>1</sup> = preferred model.
**Baseline predictors of anxiety groups**

Bivariate regression models for predictors of anxiety group membership are presented in Table 12. Compared with the no-anxiety group, the elevated-anxiety group were younger in age, more likely to be female, and of non-Anglo Celt ethnicity. The odds of experiencing elevated-anxiety symptoms were also increased for those with higher BMI, worse glycaemic control, less frequent SMBG, more insulin and antidepressant use, and for those presenting with more macrovascular complications and more regularly attending healthcare appointments. A lifetime history of generalized anxiety and major depression, were the strongest bivariate predictors of elevated-anxiety symptoms.

To determine the separable contribution of lifetime generalized anxiety and major depression, an adjusted logistic regression model was performed. Age, gender, and Anglo-Celt ethnicity were entered into the first step, with younger age (OR = 0.95, 95% CI = 0.94, 0.97) and female gender (OR = 1.56, 95% CI = 1.07, 2.29) remaining significant. In the second step, lifetime generalized anxiety was associated with a five-fold increased risk of elevated-anxiety symptoms (OR = 5.51, 95% CI = 3.67, 8.29) after age-and gender-adjustment. This relationship remained significant, but reduced, when lifetime major depression was included in the third step (lifetime generalized anxiety: OR = 2.78, 95% CI = 1.74, 4.44; lifetime major depression: OR = 4.09, 95% CI = 2.43, 6.87), with lifetime major depression emerging as the strongest predictor of elevated-anxiety group.
Table 12.

**Bivariate logistic regression models examining baseline predictors of anxiety group membership among 1,091 people with type 2 diabetes**

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Group 1: “No anxiety” (87.4%) n = 954</th>
<th>Group 2: “Elevated anxiety” (12.6%) n = 137</th>
<th>Odds Ratio (OR)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>65.5±10.5</td>
<td>59.9±11.4</td>
<td>0.96</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age at diabetes diagnosis</td>
<td>55.9±11.3</td>
<td>50.4±11.9</td>
<td>0.96</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>8.0 [2.0-15.2]</td>
<td>8.9 [3.0-15.0]</td>
<td>0.99</td>
<td>0.625</td>
</tr>
<tr>
<td>Gender, % women</td>
<td>43.9</td>
<td>61.4</td>
<td>1.59</td>
<td>0.012</td>
</tr>
<tr>
<td>Ethnicity, % Anglo Celt</td>
<td>60.0</td>
<td>51.1</td>
<td>0.70</td>
<td>0.050</td>
</tr>
<tr>
<td>English fluency, % non-fluent</td>
<td>7.2</td>
<td>9.5</td>
<td>1.35</td>
<td>0.350</td>
</tr>
<tr>
<td>Education, % primary or less</td>
<td>9.0</td>
<td>12.5</td>
<td>1.44</td>
<td>0.196</td>
</tr>
<tr>
<td>Marital status, % single</td>
<td>34.0</td>
<td>35.6</td>
<td>1.07</td>
<td>0.716</td>
</tr>
<tr>
<td><strong>Clinical characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31.1±5.7</td>
<td>33.6±6.8</td>
<td>1.07</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA₁c, mmol/mol (%)</td>
<td>6.7 [6.2-7.5]</td>
<td>7.2 [6.2-7.9]</td>
<td>1.25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting serum glucose</td>
<td>7.1 [6.1-8.4]</td>
<td>7.7 [6.3-9.8]</td>
<td>1.12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes treatment, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet/exercise</td>
<td>27.1</td>
<td>19.0</td>
<td>0.63</td>
<td>0.043</td>
</tr>
<tr>
<td>Oral glucose lowering medications (OGLMs)</td>
<td>53.5</td>
<td>46.7</td>
<td>0.76</td>
<td>0.140</td>
</tr>
<tr>
<td>Insulin only</td>
<td>3.7</td>
<td>7.3</td>
<td>2.07</td>
<td>0.050</td>
</tr>
<tr>
<td>Insulin + OGLMs</td>
<td>15.7</td>
<td>27.0</td>
<td>1.98</td>
<td>0.001</td>
</tr>
<tr>
<td>Number of medical visits in past year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Practitioner</td>
<td>3.0 [2.0-4.0]</td>
<td>4.0 [2.0-11.5]</td>
<td>1.07</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes outpatient clinic visit</td>
<td>0 [0-0]</td>
<td>0 [0-1.0]</td>
<td>1.18</td>
<td>0.002</td>
</tr>
</tbody>
</table>
Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group 1: “No anxiety” (87.4%)</th>
<th>Group 2: “Elevated anxiety” (12.6%)</th>
<th>Odds Ratio (OR)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes-related outpatient clinic visit</td>
<td>0 [0-0]</td>
<td>0 [0-1.0]</td>
<td>1.04</td>
<td>0.371</td>
</tr>
</tbody>
</table>

Self-management and health outcomes

<table>
<thead>
<tr>
<th></th>
<th>Group 1: “No anxiety” (87.4%)</th>
<th>Group 2: “Elevated anxiety” (12.6%)</th>
<th>Odds Ratio (OR)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMBG number of times per week</td>
<td>5.5 [2.0-10.0]</td>
<td>6.0 [0-14.0]</td>
<td>1.01</td>
<td>0.490</td>
</tr>
<tr>
<td>SMBG, % yes</td>
<td>87.4</td>
<td>78.3</td>
<td>0.52</td>
<td>0.005</td>
</tr>
<tr>
<td>Self and/or other monitoring of blood glucose, % yes</td>
<td>88.4</td>
<td>79.8</td>
<td>0.52</td>
<td>0.007</td>
</tr>
<tr>
<td>Smoking status, % current</td>
<td>7.6</td>
<td>8.8</td>
<td>1.18</td>
<td>0.622</td>
</tr>
<tr>
<td>Macrovascular complications, % yes</td>
<td>35.2</td>
<td>51.8</td>
<td>1.99</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy, % yes</td>
<td>58.9</td>
<td>52.6</td>
<td>0.77</td>
<td>0.158</td>
</tr>
</tbody>
</table>

Psychological characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group 1: “No anxiety” (87.4%)</th>
<th>Group 2: “Elevated anxiety” (12.6%)</th>
<th>Odds Ratio (OR)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressant use, % current</td>
<td>10.6</td>
<td>30.7</td>
<td>3.73</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lifetime generalized anxiety, % yes</td>
<td>21.7</td>
<td>63.2</td>
<td>6.18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lifetime major depression, % yes</td>
<td>29.9</td>
<td>78.3</td>
<td>8.46</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Note. Reference category = no anxiety; HbA1c = glycated hemoglobin; SMBG = self-monitoring of blood glucose; lifetime MDD = lifetime major depressive disorder; lifetime GAD = lifetime generalized anxiety disorder. Data are presented as proportions, means±standard deviations, or medians [interquartile range].
Outcomes of anxiety groups

Relative to those with no-anxiety, membership to the elevated-anxiety group predicted higher BMI (B=1.98, \( p<0.001 \)), more frequent attendance at GP (B=4.50, \( p<0.001 \)) and outpatient appointments (B=1.29, \( p=0.046 \)), and more antidepressant use at Year 4 (B=1.17, OR=3.21, \( p<0.001 \)). However, these relationships became non-significant after accounting for the severity of each variable at baseline (all \( p>0.05 \)), indicating that BMI, antidepressant use and healthcare attendance remained increased and stable over time. Anxiety group was not associated with any other clinical or self-management characteristic at Year 4 (all \( p>0.05 \)).

Overlap between anxiety and depression groups

We next investigated whether there was an overlap between elevated-anxiety symptom groups and previously determined depression groups in the same community sample (Whitworth et al., 2017). Trajectories of PHQ-9 depression symptoms were investigated similarly in the same cohort using Latent Curve Growth Analysis, and two sub-groups were found to have persistently-elevated depression symptoms, although with different patterns. Overall, 13.9% of the current sample had persistent-depression symptoms over the same time period that the anxiety trajectories were examined, and two-thirds of those in the elevated-anxiety group (n=87; 64.4%) also experienced persistent-depression during this time.

We then explored whether having elevated-anxiety alone, persistent-depression alone, or both symptoms in combination influenced the severity of anxiety. Figure 5 displays average anxiety symptom scores at each time point (baseline, Year 2 and Year
4) for individuals in the following symptom trajectory groups: anxiety trajectory alone, depression trajectory alone, both anxiety-and depression-trajectories, and neither. One-way ANOVA models were used to compare the mean severity of GADS total scores over time. As expected from the pattern of anxiety symptoms in Figure 4, the severity of anxiety fell over time for those belonging to the anxiety trajectory group, as well as for those with overlapping anxiety and depression trajectories. Mean anxiety symptoms were higher at Year 0 and Year 2 in those with overlapping anxiety and depression trajectories, compared to the group with anxiety alone (all $p<0.001$). Notably, the group with persistent depression alone had higher anxiety symptom scores than the individuals with no anxiety or depression ($p<0.001$), and this group displayed a pattern of gradually worsening anxiety symptoms over time. By Year 4, those with elevated-anxiety only, had less severe anxiety symptoms than those with comorbid depression, or depression alone ($p<0.001$).

Tests of between-group differences at Year 0, revealed that lifetime major depression and lifetime generalized anxiety were more prevalent in the combined elevated-anxiety and persistent-depression group, relative to the elevated-anxiety group alone ($p<0.001$). This group also had higher HbA1c at Year 0 relative to the other two groups ($F(2,192)=3.87$, $p=0.023$), but this relationship became non-significant after Bonferroni adjustment (both $p>0.05$).
Figure 5. Mean estimated GADS total scores in the total available sample (N=1086) for overlapping anxiety and depression groups over 4 years.
Conclusions

The present study is the first to identify trajectories of anxiety symptoms in a large, community-based cohort of individuals with type 2 diabetes. We found two distinct groups, specifically individuals with low-to-no anxiety symptoms across all time points (Group 1) and those experiencing high anxiety symptoms that began to improve but remained elevated and did not fully remit over four years (Group 2). Membership of this latter group was predicted by younger age, higher HbA1c and BMI, more macrovascular complications, insulin use, and both lifetime anxiety and depression. The presence of comorbid depression and anxiety symptoms conferred the greatest risk of a more severe pattern of anxiety. These data indicate that screening for and treating any elevated anxiety symptoms in diabetes, particularly for those with suboptimal diabetes management, chronic complications and depression, may be beneficial.

For individuals with type 2 diabetes, anxiety can be expected to peak following diabetes diagnosis and at key points during the disease course, for example at the onset of chronic complications and with initiation of insulin treatment (Trento et al., 2015; Young-Hyman et al., 2016). Current recommendations are to screen for, and treat, individuals meeting a diagnosis of GAD or scoring above a clinical cut-point for anxiety at these key stages (Young-Hyman et al., 2016). The most important finding in the present study is that, for a group of individuals with long duration disease and chronic complications (median diabetes duration of 9 years in Group 2), sub-threshold anxiety symptoms appeared to be more persistent and prevalent than previously thought and displayed a lifetime course. In the only prior study of the course of GAD in diabetes,
Fisher and colleagues (2008) identified a decreasing prevalence of GAD diagnoses over 18 months, from 6.9% to 0.7% (Fisher et al., 2008). By assessing anxiety severity over a longer follow-up period, we found that a substantially larger proportion of individuals (Group 2: 12.6%) continued to experience sub-threshold anxiety symptoms which, while also decreasing over time, remained consistently higher than in those with low-no anxiety (Group 1). While reasons for the observed decrease in anxiety symptoms are unclear, one explanation is that GAD symptoms may fluctuate and remain elevated over a longer period of follow-up, displaying the pattern of relapse and remission over time observed in the general population (Keller, 2002; Schoevers, Deeg, van Tilburg, & Beekman, 2005; Trento et al., 2015). Taken together, these findings indicate that assessing for a single DSM-IV GAD diagnosis in diabetes may under-represent those individuals experiencing ongoing psychological issues. Regular monitoring of anxiety symptoms, especially for those with lifetime generalized anxiety and/or major depression, may facilitate earlier identification of individuals in need of ongoing mood management.

An interesting finding was the significant association between diabetes management and the severity of anxiety symptoms. There is debate in the literature regarding whether less severe anxiety symptoms are associated with worse glycemic control and health-related outcomes (Anderson et al., 2002; Balhara & Sagar, 2011; Fisher et al., 2008; Trento et al., 2015) or vice versa. The present study indicates, for the first time, that worse diabetes management and glycemic control are risk factors for a more chronic underlying pattern of anxiety. While those with elevated-anxiety were not
found to have worse health outcomes or self-care at Year 4 relative to the no-anxiety group, it is likely that chronic anxiety symptoms have a more sinister long-term health impact. In community samples, sub-threshold anxiety and worry have been associated with heart failure and high blood pressure in individuals with cardiovascular disease (Grenier et al., 2012; Tully, Cosh, & Baune, 2013) and, alongside GAD, may increase insulin resistance and mortality risk due to underlying inflammatory changes (Black, 2003). These findings suggest that stepped-care treatment of any elevated anxiety symptoms over time in diabetes may minimize the long-term impact of anxiety on physiological and psychological functioning.

Another important contribution of the present study was the identification of a high pattern of overlap between anxiety and depression symptom trajectories. Both lifetime major depression and generalized anxiety were the strongest predictors of membership to the elevated-anxiety group, and individuals with recurring depression symptoms (persistent-depression group only) appeared to be particularly vulnerable to the development of anxiety over time. The present study extends, through longer follow-up, earlier findings that comorbid anxiety and depression can confer greater disability, symptom burden and severity in diabetes (Deschênes, Burns, & Schmitz, 2015). We suggest that more intensive monitoring and treatment of anxiety may be required for individuals with depression, particularly to identify those who transition between anxious-depressed states over time. As the presence of anxiety can make depression harder to treat (Merikangas et al., 2003), referral to specialist psychological services for individuals with symptoms of both disorders may be required to enable full symptomatic
recovery, with Cognitive Behavior Therapy (CBT) demonstrating efficacy in this population (Petrak, Baumeister, et al., 2015; Young-Hyman et al., 2016).

A key strength of this study was adopting a novel methodology that allowed for the observation of underlying individual trajectories of anxiety symptoms (Nagin, 2005). LGMM empirically tests how well a model fits to the data rather than deciding on a number of hypothesized groups a priori and potentially biasing interpretation (Nagin, 2005). There were also several limitations. First, the GADS was used instead of the Generalized Anxiety Disorder 7-item scale in this study (GAD-7; Kroenke, Spitzer, Williams, Monahan, & Löwe, 2007), as the GAD-7 was not available when the FDS2 was designed. We believe the GADS is an improvement on this scale as it assesses DSM-IV/5 criteria for GAD over the past 6 months, rather than a partial list of symptoms over the past 2 weeks (Starkstein et al., 2014). The GADS has demonstrated high test-retest reliability and good concordance with diagnostic interview (Starkstein et al., 2014). Second, interpretation of the overlap between depression and anxiety groups may be limited, as the PHQ-9 was administered annually and the GADS biennially. Ongoing follow-up of the overlap in, and correlates of, depression and anxiety symptom trajectories over more regular intervals is needed. Finally, we did not assess for diabetes-specific emotional distress, which refers to the complex psychological and behavioral burden associated with having diabetes (Fisher et al., 2010). It is possible that some of the longitudinal inter-relationships observed between anxiety, depression, and glycemic control may be driven by elevated levels of diabetes distress (Ehrmann et al., 2015; Fisher et al., 2010).
In conclusion, the present data show that generalized anxiety is an important comorbidity in type 2 diabetes, and is a disorder that clinicians should attend to in routine care. A sub-group of individuals were found to experience anxiety symptoms that remained elevated but below clinical cut-points over time, with anxiety symptoms more chronic for those with comorbid depression. Extending on current guidelines (Young-Hyman et al., 2016), we recommend screening for anxiety and depression severity visit-to-visit, in addition to clinical DSM-IV diagnoses, to enable earlier detection and targeted psychological intervention for these at-risk groups. Assessing lifetime major depression and generalized anxiety at diabetes diagnosis using measures such as the BLDS and GAD-LT provides another opportunity to identify and proactively monitor those at risk of worsening psychological and health-related outcomes.
Chapter 6: General Discussion

Preface

The overarching aim of this thesis was to provide an in-depth examination of the longitudinal interrelationships between depression, anxiety, and type 2 diabetes. Specific findings relating to each empirical study have been detailed in each Chapter, so they are summarized only briefly here. This general discussion then aims to examine the findings presented from their broader methodological and clinical contexts, and to consider implications for the assessment and treatment of psychological problems in type 2 diabetes.

Overview of study findings

Study 1 (Chapter 2) identified, in a representative community sample of individuals’ with T2DM, that reporting a lifetime history of GAD, as well as lifetime MDD, is a significant risk factor for more severe current anxiety and depression symptoms. A crucial finding was that individuals with a lifetime history of both disorders were at the greatest risk of reporting more severe depressive symptoms, which in turn was associated with having a higher BMI, worse glycaemic control, being less likely to perform SMBG, and a greater likelihood of currently smoking. Taken together, this study points to the chronicity of depression and anxiety in T2DM, and highlighted the importance of considering depression and anxiety as a continuous construct in diabetes.

Study 2 extended the findings of Study 1, longitudinally, and identified two sub-groups of individuals with diabetes who experienced a pattern of cycling but persistent
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depression symptoms that did not fully remit over 5 years. The most important risk-factor for this symptom course was a self-reported lifetime MDD history. Using a novel trajectory approach, the key contribution of this study is the finding that a larger number of individuals experienced ongoing subthreshold depressive symptoms than previously estimated: individuals who may be missed under current screening protocols. While these individuals had higher baseline HbA$_{1c}$ and BMI, the persistence in symptoms over time did not correspond with a worsening in glycaemic control, weight management, or frequency of SMBG.

Study 3 examined the course of anxiety symptoms in the same sample, and explored diabetes-related predictors and outcomes of this symptom course. The most important finding of this study was the identification of a group of individuals who experienced gradually improving but consistently elevated anxiety symptoms over 4 years. As in Study 2, the strongest risk factor for these symptoms was having a lifetime history of both GAD and MDD. Individuals with elevated-anxiety experienced more macrovascular complications at baseline, and were more likely to be overweight, hyperglycemic and to use insulin. However, and as in Study 2, these outcomes remained stable over the follow-up period. Of considerable clinical importance, this study identified a high overlap between the elevated-anxiety group, and the combined persistent-depression groups from Study 2. Those individuals captured by both groups had the most severe pattern of anxiety, and a number of individuals with persistent-depression developed increasing anxiety symptoms over time. Taken together, these findings indicate that the overlap between depression and anxiety likely contributes to a
more chronic pattern of anxiety symptoms, which may warrant more intensive management.

A consistent finding across all the empirical studies in this thesis, is the importance of considering the severity of depression and anxiety symptoms, in addition to clinical diagnoses and diagnostic thresholds, longitudinally in diabetes. This broader symptom perspective contributes to three key areas of knowledge: (1) our understanding of the course of depression and anxiety in T2DM; (2) conceptualization and measurement of the overlap between depression and anxiety; and (3) the strength of developmental interrelationships between mood disturbance and diabetes. Each area is discussed in turn, below, followed by implications of these findings for the screening, monitoring, and treatment of psychosocial issues in diabetes. Finally, future directions are explored.

**Understanding the course of depression and anxiety in T2DM**

Two decades ago, it was proposed that “the inclusion of subthreshold categories of depression dramatically improves the coverage of treated depression, and better enables the characterization of its longitudinal course” (Angst & Merikangas, 1997). However, a broader examination of the course of depression and anxiety symptom severity in type 2 diabetes has not been undertaken, representing a significant gap in our knowledge. This thesis addresses that gap. A key finding is that a larger proportion of individuals experienced ongoing but sub-threshold depression and anxiety symptoms over time, than previous cross-sectional and longitudinal estimates of MDD and GAD diagnoses (Fisher et al., 2008). These findings support the need to consider prevalence
over multiple assessments (Fisher et al., 2008; Schmitz et al., 2014), and suggest that conceptualizing mood more broadly from a longitudinal symptom framework, may improve the detection of individuals experiencing psychological difficulties in this population.

Across all studies, an underlying chronicity and recurrence to the experience of psychological symptoms was observed. The severity of both depression and anxiety symptoms fluctuated over time, and frequently fell below clinical cut-points: but only just. This symptom course supports the transition between threshold and sub-threshold diagnoses observed in the general population (Angst & Merikangas, 1997; Merikangas et al., 2003; Schoevers et al., 2005), and has substantial implications for individuals with type 2 diabetes. First, Study 2 suggests that an initial reduction in depression symptoms does not necessarily translate into longer-term improvements. Second, screening only for individuals meeting clinical depression and anxiety diagnoses or scoring above clinical cut-offs, may overlook those with less severe symptoms, who are at-risk of poorer health or quality of life over time (Schmitz et al., 2014). Taken together, this thesis implies that routine tracking of continuous depression and anxiety symptom scores, in addition to ongoing mood management, may be of particular benefit in this population.

Finally, taking a life-course perspective to the experience of psychological dysfunction revealed a long-standing pattern to mood problems in this large, community cohort. A self-reported, prior episode of lifetime major depression, generalized anxiety, or both, were the strongest risk factors for more severe and recurring mood symptoms in
all studies. This effect held even after accounting for diabetes-specific characteristics. Thus, these findings consistently underscore the need for detection of both lifetime depression and anxiety at diabetes diagnosis. Brief, self-report measures such as the BLDS and GAD-LT have demonstrated utility in this group, but require further validation.

The depression-anxiety comorbidity in T2DM: implications for conceptualization and measurement

Historically, major depression has been studied as the most debilitating psychological condition to affect individuals with type 2 diabetes. Extending longitudinally on recent research (Collins et al., 2009; Deschênes et al., 2015; Starkstein et al., 2014), Studies 1 and 3 provide compelling evidence that this population is vulnerable to experiencing comorbid depression and anxiety over time. These findings replicate the strong life-course association found between MDD and GAD (Merikangas et al., 2003; Schoevers et al., 2005), and question how we conceptualize and measure these disorders more broadly.

There is ongoing debate in the field of psychiatry as to whether MDD and GAD are actually separable constructs, given the frequent rates of comorbidity observed, in addition to their shared genetic and environmental risk factors (Goldberg, 2010; Watson, 2005). It has, instead, been proposed that MDD and GAD should be conceptualized similarly under a class of “distress disorders”, which share common variance in addition to unique symptoms (Watson, 2005). Given this similarity, conceptualization of either
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However, it has also been suggested that the symptom overlap between depression and anxiety, including tiredness, concentration issues and difficulty sleeping (Starkstein et al., 2014), may drive some of the observed associations (van Loo, Schoevers, Kendler, de Jonge, & Romeijn, 2016). To address this argument, Starkstein and colleagues (2014) adopted a data-driven approach to identify classes of individuals with T2DM based on the overlap in PHQ-9 and GADS symptoms, after excluding anxiety symptoms that were shared with depression (Starkstein et al., 2014). Two classes of individuals were identified with a high comorbidity of depression and anxiety symptoms (termed major anxious-depression and minor anxious-depression by the authors). Similar to this thesis, both groups had poorer diabetes-related outcomes relative to those without depression and anxiety symptoms (Starkstein et al., 2014), and a greater long-term risk of cardiovascular disease (CVD) compared with groups based on DSM-IV/5 diagnoses (Bruce, Davis, Dragovic, & Starkstein, 2016). Taken together, it appears that the overlap between depression and anxiety in diabetes, thus reflects a unique group of individuals experiencing greater symptom burden and severity (Deschênes et al., 2015; Schoevers, Beekman, Deeg, Jonker, & van Tilburg, 2003), which is unlikely to be explained by shared items only.

Viewing comorbidity in this way has important implications for diabetes care. These findings suggest that assessment of depression alone in this population is unlikely to be sufficient. Further, the data presented highlight the need to recognize that
individuals who present with symptoms of one disorder are likely to develop or experience worsening in the other, over time. Practitioners should be mindful of this transition, and consider routinely assessing for symptoms of both disorders, even when one may not be present at a previous assessment. Early and intensive psychosocial intervention is likely to be needed for those experiencing this overlap, to promote long-term remission in both disorders (Deschênes et al., 2015; Schoevers et al., 2005).

**Implications for the strength of developmental interrelationships between mood and T2DM**

There is extensive debate in this field relating to whether the severity, rather than diagnosis of depression and anxiety symptoms, affects diabetes self-management, glycaemic control, and health complications (Anderson et al., 2002; Fisher et al., 2010; Gonzalez et al., 2007; Snoek, Bremmer, & Hermanns, 2015). All studies make a substantial contribution by indicating that there exist significant, developmental relationships between the course and severity of depression and anxiety symptoms, and a range of diabetes-related outcomes. Two primary pathways of interest are considered below.

**Pathway 1: the course of psychological symptoms affects diabetes management and control.** Study 1 identified a significant association between continuous PHQ-9 total scores, and both diabetes management and HbA1c. This extends on earlier findings that a one-point increase in depression severity corresponds to poorer adherence to self-care and medication recommendations (Gonzalez et al., 2007), even after accounting for diabetes distress (Gonzalez, Delahanty, Safren, Meigs, & Grant,
2008), but contrasts with other studies. Notably, Fisher and colleagues (2010) found that the association between continuous depression scores and HbA1c became non-significant after accounting for a range of diabetes-related factors, including comorbid complications, diabetes distress, diet and exercise (Fisher et al., 2010). We would argue that covarying for these factors, which are known to be related to depression symptoms (de Groot et al., 2001; Gonzalez et al., 2007), may have excluded important information on this relationship, effectively removing the very variance of interest.

The chronicity of depression and anxiety in this population appeared to be a particular risk factor for poorer health. Lifetime major depression and generalized anxiety, especially when comorbid, conferred the greatest risk of poorer outcome by increasing the severity of current depressive symptoms. A number of pathways may explain this association. First, lifetime MDD and GAD may contribute, through biopsychosocial factors, to an increased risk of diabetes onset (Edwards & Mezuk, 2012; Engum, 2007; Katon, 2003) and difficulty adapting to diabetes diagnosis (Katon, 2003). In turn, this chronicity in psychological symptoms may continue to contribute, over time, to a worsening in disease severity through underlying inflammatory, immune and endocrine changes (Black, 2003; Gonzalez, Safren, et al., 2008; Windle & Windle, 2013). Taken together, these findings suggest that individuals with a history of depression or anxiety, and more severe current depression symptoms, may benefit particularly from early diabetes education and adherence training, to maximize engagement in successful diabetes self-management (Davies et al., 2008).
Pathway 2: the severity of diabetes affects the course of psychological symptoms. The findings from Studies 2 and 3 offer compelling, prospective evidence that, in addition to clinical diagnoses (Schmitz et al., 2013; Trento et al., 2015), diabetes which is more severe and insufficiently managed confers significant risk for ongoing, subthreshold and non-remitting mood symptoms. Shared associates of ongoing subthreshold depression and anxiety included worse glycaemic control, higher BMI, and more attendance at healthcare appointments. Less frequent self-management, more insulin use, and more macrovascular complications were also predictive of ongoing, subthreshold anxiety symptoms. A number of mechanisms may contribute to these associations. Fear of further health complications and/or hypoglycaemia, which can result from difficulties managing HbA$_1$c levels, may worsen or maintain anxiety (Wild et al., 2007). Common factors shared between depression, anxiety, and diabetes, including obesity, inflammation and socio-economic disadvantage, may also contribute to psychological dysfunction over time (Everson et al., 2002; Tabák et al., 2014). These findings indicate a particular need to screen for the presence of sub-threshold mood symptoms, for individuals experiencing chronic diabetes complications and hyperglycaemia.

Despite these proposed pathways by which mood symptoms and diabetes may be interrelated over time, longitudinal examination over 4-years did not reveal any significant worsening in BMI, glycaemic control, or SMBG. Thus, the underlying recurrence of psychological symptoms did not appear to contribute further to poorer outcomes in this population. One explanation for these results is that mood severity is
not associated with long-term changes in glycaemic control (Fisher et al., 2010). A more plausible explanation is that individuals with elevated-anxiety and persistent-depression already tended to be overweight, and to have worse glycaemic control and diabetes self-management at baseline. For individuals with established diabetes, these factors, which are common to both mood problems and T2DM (Tabák et al., 2014), tend to remain chronic. Thus, a ceiling effect may have occurred, with limited room for outcomes to worsen in these groups. However, it is also possible that a longer period of follow-up may reveal a worsening in outcomes associated with ongoing, subthreshold depression and anxiety symptoms. Irrespective of this, it appears that preventive measures aimed at targeting factors such as weight, smoking, and sedentary activity prior to the onset of both diabetes and mood problems, may be the most promising method for improving long-term health in this population.

In summary, all studies of this thesis reflect the same theme: that there exists a clinically relevant and likely under-recognized relationship between the course and severity of an individuals’ psychological symptoms and health-related outcomes in T2DM.

Clinical implications

Studies 2 and 3 were among the first to identify heterogeneous trajectories of depression and anxiety symptoms in diabetes, and to demonstrate deleterious relationships between the continuous severity of mood symptoms, and glycaemic control, self-management and obesity. The findings of all experimental studies have
important implications for the screening, monitoring and treatment of psychological symptoms in this population.

**Screening for depression and anxiety.** While all clinical guidelines now recommend routinely screening for depression and anxiety at primary care appointments (International Diabetes Federation Clinical Guidelines Task Force, 2012; Young-Hyman et al., 2016), rates of case detection are notoriously low (Pouwer, 2009; Tylee & Walters, 2006). The findings from this thesis suggest a further complicating factor in this process may be the reliance on identifying ‘cases’ of MDD and GAD (American Diabetes Association, 2017; Young-Hyman et al., 2016), at the expense of considering the broader experience of psychological distress (Fisher et al., 2014). This may under-detect those individuals experiencing persistently elevated but sub-threshold mood symptoms. A number of recommendations regarding the nature and timing of psychological screening processes in this population, arise from this work.

First, the diagnosis of diabetes is a critical time for any individual, involving a comprehensive medical and lifestyle assessment to confirm diagnosis (American Diabetes Association, 2017). As previously discussed, we recommend incorporating brief screening measures of both lifetime and current depression and anxiety into this assessment. At this stage, individuals reporting a history of psychological problems can be flagged as at-risk. Based on our findings, individuals presenting with more complex weight management issues, hyperglycaemia, and more diabetic complications at diabetes diagnosis, should also be flagged as requiring more proactive diabetes and mood management.
Second, we recommend that, at annual healthcare assessments of diabetes complications and management, the continuous severity of depression and anxiety symptoms using instruments such as the PHQ-9 and GADS, be re-assessed for these at-risk groups. By monitoring more gradual patterns of symptom change, an earlier response to symptomatic worsening can be made, before a larger deterioration in psychological or metabolic status occurs (American Diabetes Association, 2017). This is particularly relevant for individuals who transition between depression and anxiety states over time. If an individual presents with sub-threshold psychological symptoms over two or more assessments, this may indicate the need for psychosocial intervention (Pouwer, 2009).

**Treatment of depression and anxiety: an integrated approach.** International guidelines support a patient-centered approach to diabetes care, which addresses the psychosocial barriers that interfere with the person’s ability to carry out diabetes self-management (American Diabetes Association, 2017; International Diabetes Federation Clinical Guidelines Task Force, 2012). This thesis indicates that treatment of those with sub-threshold and chronic depression and anxiety symptoms, particularly if they also have lifetime MDD or GAD, may be required to achieve optimal diabetes control. These data also suggest that supporting individuals to cope with the symptoms of anxiety may prevent the later development or worsening in depression for a sub-group of this population. However, the best treatment approach for those who do not fall into traditional diagnostic categories is currently not clear. A brief review of best-practice
evidence for the treatment of psychosocial problems in T2DM, and implications of the present research, is presented below.

**Which psychosocial treatments are effective in T2DM?** A range of psychological therapies offer promise for the treatment of depression and anxiety in diabetes. Cognitive Behaviour Therapy (CBT; Petrak, Herpertz, et al., 2015; Safren et al., 2014; van der Feltz-Cornelis et al., 2010) psycho-education (Penckofer et al., 2012), and selective-serotonin reuptake inhibitors (SSRIs) for more severe depression symptoms (Lustman, Freedland, Griffith, & Clouse, 2000; Petrak, Baumeister, et al., 2015), have demonstrated effectiveness. Diabetes-specific CBT and Mindfulness-Based Cognitive Therapy (MBCT) have also shown utility for improving elevated depressive symptoms and emotional distress, for those without clinical diagnoses of MDD (Hermanns et al., 2015; van Son et al., 2013). Whether these approaches can be extended to treat sub-threshold mood symptoms warrants further investigation.

Further, there is extensive debate regarding whether the treatment of mood translates to an improvement in glycaemic control (Hermanns et al., 2015; Markowitz, Gonzalez, Wilkinson, & Safren, 2011; van der Feltz-Cornelis et al., 2010). Growing evidence suggests that interventions which integrate psychosocial and self-management strategies may be more effective in improving mood, self-care, and HbA$_1c$ (Bogner, Morales, de Vries, & Cappola, 2012; Safren et al., 2014; van der Feltz-Cornelis et al., 2010). In addition to mood, psychosocial targets in these interventions frequently include: diabetes-specific distress; understanding of glycaemic control and how to self-manage; fear of diabetes complications and hypoglycaemia; self-efficacy relating to
diabetes self-management; and specific beliefs relating to diabetes (Aljasem, Peyrot, Wissow, & Rubin, 2001; Chao, Nau, Aikens, & Taylor, 2005; Fisher et al., 2014; Padgett, 1991; Paschalides et al., 2004; Snoek et al., 2015). Findings from the DESMOND trial indicate that even a brief, self-management program following diabetes diagnosis is effective in improving health behaviour, weight management, depression symptoms, understanding of illness, and perceptions of responsibility for diabetes management (Davies et al., 2008). This thesis posits that extending these programs more specifically to target elevated depression and anxiety symptoms early in the diabetes disease process, and to incorporate routine monitoring of treatment uptake and symptomatic improvement, will likely be beneficial.

**How should we offer treatment to at-risk individuals?** While the discussed therapies offer significant promise, issues of follow-through frequently arise after screening, due to a lack of structured and collaborative follow-up (Holt & van der Feltz-Cornelis, 2012). To resolve this issue, stepped-care management approaches for depression have been proposed to align each individual’s current presentation with graded treatment and referral pathways (Gonzalez et al., 2011; Petrak, Baumeister, et al., 2015). We propose that an extension to this approach will be particularly useful for individuals identified as at-risk in the present data.

First, at the primary care level, individuals with more mild psychological symptoms may initially benefit from a discussion and normalization of the common emotional reactions to diabetes, and provision of self-help materials (Gonzalez et al., 2011; Petrak, Baumeister, et al., 2015). Assessment of the content of psychological
distress, for example whether symptoms are related specifically to diabetes or to other life stressors (Fisher et al., 2014), may also facilitate cost-effective multidisciplinary management within existing diabetes care centers (Gonzalez et al., 2011). This may be sufficient to improve mood.

For individuals who do not show symptomatic improvement at the first step, there is currently no clear guidance regarding how severe psychological symptoms should be to warrant referral to a psychologist or mental health practitioner. The evidence presented here indicates that those with any ongoing and persistently elevated depression or anxiety symptoms, and who have issues with diabetes self-management and/or adjusting to changes in the severity of their disease (Snoek et al., 2015; Young-Hyman et al., 2016), should be referred. Referral earlier than previously recommended (Young-Hyman et al., 2016), rather than waiting for symptoms to rise to the point of meeting a clinical cut-off, may also facilitate faster recovery. At this step, evidence indicates that psychotherapy specific to mood and diabetes, of which CBT currently has the best support, in addition to possible antidepressant prescription (Petrak, Baumeister, et al., 2015), should be offered. Ongoing monitoring of treatment uptake and modification of therapy is essential (Petrak, Baumeister, et al., 2015).

In conclusion, ongoing screening, monitoring, and early stepped-care intervention is likely to be useful for individuals with persistent, sub-threshold depression and anxiety symptoms. Future research will benefit from a detailed evaluation of the effectiveness of collaborative psychological and self-management interventions for these subthreshold mood symptoms, particularly in the treatment of
comorbid depression and anxiety. Determining whether altering the long-term trajectory of mood symptoms, translates into an improvement in diabetes-related outcomes and health-related quality of life, is of particular clinical interest.

**Future directions**

The overlap between mood symptoms and diabetes distress. Diabetes distress refers to the complex psychological and behavioural burden associated with having diabetes (Fisher et al., 2010; Polonsky et al., 2005). Diabetes distress is most commonly measured using the Diabetes Distress Scale (DDS; Polonsky et al., 2005) or the Problem Areas in Diabetes Scale (PAID; Polonsky et al., 1995), and taps into domains of interpersonal, emotional, regimen-related, and physician-related distress (Polonsky et al., 2005). As such, diabetes distress reflects a broader affective experience to that captured by depression and anxiety symptom measures (Fisher et al., 2014). At the time of the FDS2 study design, diabetes distress was a newly developed construct for studying the emotional concomitants of T2DM, and was, thus, not included as part of routine FDS2 measurement. Since then, a large body of research now supports diabetes distress as an important, separable and longitudinal predictor of diabetes self-care and clinical outcomes, including glycaemic control (Fisher et al., 2010; Gonzalez, Delahanty, et al., 2008).

There is also evidence for considerable overlap between depression and diabetes distress. Recent studies have identified a cyclical relationship between the two, whereby higher levels of depression symptoms predict later diabetes distress, which then contributes to a worsening in depression, and vice versa (Burns, Deschênes, & Schmitz,
Depression and Anxiety in T2DM. There exists debate within the field as to whether depression is a separate risk factor for poorer outcome, or whether the poor self-management commonly associated with depression is actually mediated by exacerbations in diabetes distress (Fisher et al., 2010; Snoek et al., 2015). Finally, a recent study identified separable trajectories of diabetes distress that were similar to the depression groups in Study 2, further highlighting a potential, long-term overlap between these constructs (Lipscombe, Burns, & Schmitz, 2015). While understudied, overlap between anxiety and diabetes distress is expected. Thus, diabetes distress may confound some of the associations observed between depression, anxiety and diabetes-related outcomes presented in this thesis. Future research will benefit from a comprehensive examination of the overlapping and additive effects of depression, anxiety and diabetes distress trajectories, to delineate where, when, and what intervention is most warranted.

Understanding the mechanisms of change. It was beyond the scope of this thesis to examine specific mechanisms underlying the relationships between depression, anxiety and diabetes across time. Further, the full spectrum of diabetes self-care behaviours associated with mood (Gonzalez et al., 2007) were not addressed. In order to more accurately inform intervention targets for individuals with recurring, sub-threshold mood symptoms, identifying the factors which underlie how psychological symptoms and diabetes-related outcomes interact for these groups will be beneficial. For example, are changes mediated by biological inflammatory or endocrine pathways, onset of broader life stressors, beliefs about diabetes and diabetes distress, and/or difficulties
engaging in self-care (Collins et al., 2009; Everson et al., 2002; Fisher et al., 2014; Tabák et al., 2014; Tully et al., 2016)?

A promising statistical method to delineate these mechanisms is longitudinal, cross-lagged, autoregressive study designs. This method accounts for the temporal order of longitudinal data by examining whether variable $X$ at time $t$, causes variable $Y$ at time $t + 1$ and, by extension whether variable $Y$ at time $t$ causes variable $X$ at time $t + 1$ (Pakpahan, Hoffmann, & Kröger, 2017). Mediating effects can also be modelled, to address whether the pathways between $X$ and $Y$ over time are via another mechanism. This method has been adopted recently to examine mechanisms underlying the reciprocity between depressive symptoms and HbA1c across time (Schmitz, Deschênes, Burns, & Smith, 2016), as well as between depression and diabetes distress (Burns et al., 2015; Ehrmann et al., 2015). For example, Schmitz and colleagues (2016) found depressive symptoms at one time point, predicted higher HbA1c 4-years later, and this effect was mediated by lifestyle-related factors at year 2 (Schmitz et al., 2016). We recommend modeling cross-lagged relationships between emotional distress and diabetes self-care/control routinely following diabetes diagnosis, to capture the mechanisms by which mood symptoms may worsen or change at expected points in the disease process (Snoek et al., 2015), and further impact health-related outcomes. This is particularly relevant for those identified as falling into an “at risk” trajectory.

**Continuous mood symptoms: what are we actually measuring?** Another unanswered question of this thesis is: what does a change in symptom severity score truly mean? For example, does a reduction of $X$ points on a depression scale translate to
a meaningful improvement in the experience of depression for that individual (Fried, 2016)? The findings presented here suggest that ongoing change and persistence in psychological symptom severity appears to be associated with adverse outcome. However, conclusions regarding the nature and impact of the symptoms experienced cannot be drawn. Recent research posits that as depression is not a uni-dimensional construct (Fried, 2015; Fried & Nesse, 2015), examination of the pattern or network of symptoms experienced over time may be more meaningful than considering overall symptom severity (Fried, 2015; Fried, Epskamp, Nesse, Tuerlinckx, & Borsboom, 2016; Snoek et al., 2015). This is supported by the finding that separate depression symptoms may differentially impact glycaemic control (Bot et al., 2013). A detailed, phenomenological examination of whether there are distinct profiles of individuals who endorse a particular pattern of depression, anxiety and distress symptoms will be revealing. Indeed, this is currently underway in the FDS2 cohort. Implications of different symptom profiles across time on psychosocial and health-related outcomes will likely be clinically informative and may help to tailor more individualized treatments.

The discourse of psychological dysfunction in T2DM. This thesis has emphasized the breadth of psychological experience for individuals with diabetes, and proposed that sub-threshold psychological symptoms still play an important role in long-term health behaviour. As a result, a review of the discourse relating to psychopathology in chronic disease populations, and how this affects access to care, is needed. Distress is often pathologised (Gonzalez et al., 2011), which can facilitate a fear of stigma surrounding mental health problems, and limit the individual’s likelihood of accessing
support. Facilitated discussion between the individual and their healthcare provider about the broader relationship between diabetes and elevated emotional distress, of which more severe depression and anxiety may be a part, may assist in reducing stigma and improving rates of symptom detection and treatment (Barnard, Peyrot, & Holt, 2012; Fisher et al., 2014; Holt et al., 2016). Further, improvements in training programs for the healthcare professional that emphasize the importance of dealing with a spectrum of emotional issues in routine care, and of accounting for the values, preferences, and priorities of the individual, may assist in improving early screening and referral to stepped-care treatment (Holt et al., 2016).

**Concluding statements**

This thesis examined, for the first time in a large community cohort of individuals with clinically diagnosed T2DM, the complex interplay between depression, anxiety, and diabetes over time. Lifetime generalized anxiety, in addition to depression, emerged as an important predictor of later psychological symptomatology and diabetes self-management. Most notably, the findings presented here indicate a chronic, underlying pattern of cycling depression and anxiety symptoms for a sub-set of this population, which frequently fall below clinical cut-offs and likely remain untreated or under-treated. Importantly, the mechanisms that underlie the relationship between long-standing mood symptoms and diabetes self-management and control remain to be clarified.

The title of this thesis posed the question “depression and anxiety symptoms in type 2 diabetes mellitus: a matter of time?” The answer provided by all studies presented
here is: yes. Extending our examination of depression and anxiety to a broader symptomatic experience which develops and changes over the course of type 2 diabetes, provides a novel and clinically meaningful perspective on the relationships between mood and diabetes-related health outcomes. Without an appreciation of the individual’s history and development, predictions of future functioning will be inherently limited.
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Appendix A: Table A1

The below material was provided as an online supplement for Chapter 2.

Table A1.

Non-significant indirect mediation models testing the direct (path c') and indirect (path ab) effect of lifetime anxiety on diabetes management/control, via the severity of current mood symptoms. Data are presented as regression coefficients (B; 95% confidence interval)

<table>
<thead>
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<th>Model</th>
<th>Predictor</th>
<th>Mediator</th>
<th>Outcome</th>
<th>Path a</th>
<th>Path b</th>
<th>Path ab: Indirect effect of L-GAD on outcomes</th>
<th>Path c: Total effect of L-GAD on outcomes</th>
<th>Path c': Direct effect of L-GAD on outcomes, accounting for current mood severity</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>L-GAD</td>
<td>PHQ-9 score₁</td>
<td>HbA₁c</td>
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<td>B₁ = 0.02</td>
<td>B₁ = 0.03 (-0.02 to 0.09)</td>
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<td>B = -0.22</td>
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<tr>
<td></td>
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<td>B₂ = -0.01</td>
<td>B₂ = -0.02 (-0.13 to 0.09)</td>
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<td>GADS score&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Smoking status</td>
<td>GADS score&lt;sub&gt;2&lt;/sub&gt;</td>
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<td></td>
<td></td>
<td></td>
<td>(-0.24 to 0.05)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>GADS score&lt;sub&gt;2&lt;/sub&gt;</td>
<td>B₂ = 3.50‡</td>
<td>B₂ = 0.04</td>
<td>B₂ = 0.14</td>
<td>(-0.12 to 0.45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>L-GAD</td>
<td>PHQ-9 score&lt;sub&gt;1&lt;/sub&gt;</td>
<td>B₁ = 1.43‡</td>
<td>B₁ = 0.10</td>
<td>B₁ = 0.14</td>
<td>B = -21.60</td>
<td>B = -21.62</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>(-0.03 to 0.37)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>GADS score&lt;sub&gt;2&lt;/sub&gt;</td>
<td>B₂ = 3.21‡</td>
<td>B₂ = -0.04</td>
<td>B₂ = -0.12</td>
<td>(-0.54 to 0.38)</td>
<td></td>
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</tr>
</tbody>
</table>

*Note.* L-GAD = lifetime generalized anxiety disorder; PHQ-9 = Patient Health Questionnaire-9 item version; GADS = Generalized Anxiety Disorder Scale; B = regression coefficient; a = association between the L-MDD/L-GAD and current mood symptoms; b = association between current depression/anxiety symptom severity and diabetes outcomes; ab = test of the indirect effect of lifetime history on outcomes via current mood symptom severity; c = total effect of L-MDD/L-GAD on the outcome variable (path ab + path c'); c' = direct effect of L-MDD/L-GAD on the outcome variable, after accounting for the current mood symptom severity;

<sup>1</sup> = PHQ-9 scores as the mediator.
<sup>2</sup> = GADS scores as the mediator.

† = significant at p < .05. ‡ = significant at p < .001.
Appendix B: Table B1

The below material was provided as an online supplement for Chapter 4.

Table B1. 
*Single growth curve model building for BMI, HbA1c, and self-monitoring of blood glucose at Year 0, 2 and 4*

<table>
<thead>
<tr>
<th>Model</th>
<th>Diabetes-management</th>
<th>$\chi^2$</th>
<th>df</th>
<th>$p$</th>
<th>AIC</th>
<th>Parsimony ratio (90% CI)</th>
<th>RMSEA (90% CI)</th>
<th>CFI</th>
<th>TLI</th>
<th>SRMR</th>
<th>Growth parameter estimates</th>
<th>Growth parameter estimates</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intercept</td>
<td>Mean</td>
</tr>
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<td></td>
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<td></td>
<td>Mean</td>
<td>Var</td>
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<td></td>
<td></td>
<td>Slope</td>
<td>Mean</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Var</td>
<td>Var</td>
</tr>
<tr>
<td>Intercept only</td>
<td>BMI</td>
<td>22.44</td>
<td>4</td>
<td>&lt;0.001</td>
<td>16370.82</td>
<td>0.28</td>
<td>0.06 (0.04-0.09)</td>
<td>0.99</td>
<td>0.99</td>
<td>0.06</td>
<td>31.38†</td>
<td>34.92†</td>
</tr>
<tr>
<td>Linear change*</td>
<td>BMI</td>
<td>1.80</td>
<td>1</td>
<td>0.18</td>
<td>16356.18</td>
<td>0.07</td>
<td>0.03 (0-0.09)</td>
<td>1.00</td>
<td>0.99</td>
<td>0.00</td>
<td>31.41†</td>
<td>35.07†</td>
</tr>
<tr>
<td>Logarithmic change</td>
<td>BMI</td>
<td>2.90</td>
<td>1</td>
<td>0.09</td>
<td>16357.29</td>
<td>0.07</td>
<td>0.04 (0-0.10)</td>
<td>1.00</td>
<td>0.99</td>
<td>0.00</td>
<td>31.40†</td>
<td>35.89†</td>
</tr>
<tr>
<td>Intercept only</td>
<td>HbA1c</td>
<td>17.88</td>
<td>4</td>
<td>&lt;0.001</td>
<td>10040.88</td>
<td>0.27</td>
<td>0.05 (0.03-0.08)</td>
<td>0.99</td>
<td>0.99</td>
<td>0.06</td>
<td>7.17†</td>
<td>1.24†</td>
</tr>
<tr>
<td>Linear change</td>
<td>HbA1c</td>
<td>1.69</td>
<td>1</td>
<td>0.19</td>
<td>10030.68</td>
<td>0.07</td>
<td>0.02 (0-0.09)</td>
<td>0.99</td>
<td>0.99</td>
<td>0.01</td>
<td>7.14†</td>
<td>1.34†</td>
</tr>
<tr>
<td>Logarithmic change*</td>
<td>HbA1c</td>
<td>0.79</td>
<td>1</td>
<td>0.38</td>
<td>10029.78</td>
<td>0.07</td>
<td>0 (0-0.07)</td>
<td>1.00</td>
<td>1.00</td>
<td>0.00</td>
<td>7.13†</td>
<td>1.47†</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept only</td>
<td>Self-monitoring</td>
<td>20.45</td>
<td>4</td>
<td>&lt;0.001</td>
<td>22262.54</td>
<td>0.27</td>
<td>0.06 (0.04-0.09)</td>
<td>0.97</td>
<td>0.98</td>
<td>0.04</td>
<td>7.44†</td>
<td>35.74†</td>
</tr>
<tr>
<td>Linear change*</td>
<td>Self-monitoring</td>
<td>1.03</td>
<td>1</td>
<td>0.31</td>
<td>22249.12</td>
<td>0.07</td>
<td>0.01 (0-0.08)</td>
<td>1.00</td>
<td>1.00</td>
<td>0.01</td>
<td>7.33†</td>
<td>40.69†</td>
</tr>
<tr>
<td>Logarithmic change</td>
<td>Self-monitoring</td>
<td>1.41</td>
<td>1</td>
<td>0.24</td>
<td>22249.50</td>
<td>0.07</td>
<td>0.02 (0-0.08)</td>
<td>0.99</td>
<td>0.99</td>
<td>0.01</td>
<td>7.36†</td>
<td>46.31†</td>
</tr>
</tbody>
</table>

Note. AIC = Akaike Information Criterion (lower score = better fit); Parsimony ratio is defined as df / [0.5k(k+1)] where k is the number of observed variables; RMSEA = Root Mean Square Error Of Approximation (<0.06 = good fit); CFI = Comparative Fit Index; TLI = Tucker Lewis Index (>0.95 = good fit); SRMR = Standard Root Mean Square Residual (<0.05 = good fit); * preferred model. † = $p < 0.05$. 
Appendix C: Table C1

The below material was created as an online supplement for Chapter 5.

Table C1.

**Single growth curve model building for GADS severity scores (N = 1091)**

<table>
<thead>
<tr>
<th>Model</th>
<th>$\chi^2$</th>
<th>df</th>
<th>$p$</th>
<th>AIC</th>
<th>Parsimony ratio</th>
<th>RMSEA (90% CI)</th>
<th>CFI</th>
<th>TLI</th>
<th>SRMR</th>
<th>Growth parameter estimates</th>
<th>Intercept Mean</th>
<th>Var</th>
<th>Slope Mean</th>
<th>Var</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept only</td>
<td>33.76</td>
<td>4</td>
<td>&lt;0.001</td>
<td>17178.52</td>
<td>0.27</td>
<td>0.08 (0.06-0.12)</td>
<td>0.97</td>
<td>0.98</td>
<td>0.05</td>
<td>5.29†</td>
<td>15.09†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linear change†</td>
<td>0.19</td>
<td>1</td>
<td>0.66</td>
<td>17150.95</td>
<td>0.07</td>
<td>0 (0-0.06)</td>
<td>1.00</td>
<td>1.00</td>
<td>0.00</td>
<td>5.61†</td>
<td>18.61†</td>
<td>-0.17†</td>
<td>0.62†</td>
<td></td>
</tr>
<tr>
<td>Logarithmic change model</td>
<td>2.12</td>
<td>1</td>
<td>0.15</td>
<td>17152.88</td>
<td>0.07</td>
<td>0.03 (0-0.09)</td>
<td>0.99</td>
<td>0.99</td>
<td>0.01</td>
<td>5.62†</td>
<td>21.79†</td>
<td>-0.88†</td>
<td>24.41</td>
<td></td>
</tr>
</tbody>
</table>

*Note. AIC = Akaike Information Criterion (lower score = better fit); parsimony ratio is defined as df / [.5k(k+1)] where k is the number of observed variables; RMSEA = Root Mean Square Error Of Approximation (<0.06 = good fit); CFI = Comparative Fit Index (>0.95 = good fit); TLI = Tucker Lewis Index (>0.95 = good fit); SRMR = Standard Root Mean Square Residual (<0.05 = good fit).

† = preferred model.

$\dagger = p < 0.05.$
Appendix D: ROC Curve Analysis

This Appendix details the methodology and collection of GADS data for the Receiver Operating Characteristic (ROC) curve analysis reported in Chapter 5 (Study 3). As a significant contribution of this PhD research, the student undertook a sub-study to identify an optimal cut-point for this self-report anxiety scale, for use in type 2 diabetes samples.

Participants and procedures

A stratified sample of participants from the FDS2 were recruited to take part in a study titled “How does Mood or Worry Influence Type 2 Diabetes and Its Management?” between July 2014 and January 2015. Participants were initially mailed a letter and information sheet inviting them to contact the researcher if they were/were not interested. For those who did not phone, the researcher then followed up 1 week later with a phone call to gauge interest. For those who consented to participate, individuals were posted a questionnaire pack including the GADS, to complete prior to an in-person clinical interview undertaken at Fremantle Hospital or the participant’s home. At the in-person assessment, the Anxiety-Disorders Module of the Structured Clinical Interview for Diagnostic and Statistical Manual-IV (SCID-RV-TV) was completed. The scoring of all interviews was coded by the student, and cross-checked by Professor Sergio Starkstein, an experienced Psychiatrist. The questionnaire pack included assessment of other psychosocial variables, but inclusion of these was deemed beyond the scope of the present thesis.
In total, 139 participants from the FDS2 were contacted, of whom 30.9% declined to participate, 22.3% were unable to be contacted, and 46.8% (n=65) participated. Of those who participated, 3 individuals completed the questionnaire pack only, and the clinical interview was deemed invalid for another 3. Complete GADS and SCID data for validation were available for a total of 57 individuals (87.7% of those who participated). Mean age of the sample was 63±6.1 years, median disease duration was 13 [7.5-20.4], and 45% were male.

**GADS ROC curve analysis**

Analyses was performed using SPSS Version 23 and Graphpad Prism 6. The GADS demonstrated high internal consistency (Cronbach’s a = 0.91). ROC curve analysis was performed to determine the most appropriate GADS cut-point for clinically meaningful anxiety symptoms. A cut-off of between 10 and 16 were compared based on sensitivity, specificity and the diagnostic odds ratio (see Table D1). The Youden index (representing the ideal cut-off point of maximum distance from chance level which optimizes sensitivity and specificity) and area under the curve (Figure D1) were also inspected. Table D1 indicates that a cut-off of 15 was the most clinically meaningful, resulting in the highest sensitivity and specificity, and highest diagnostic odds ratio. This number was the furthest point from chance level (best Youden index) on the ROC curve (Figure D1). This cut-off also resulted in an area under the curve of 0.93, indicating that 93% of individuals who met GAD criteria on the SCID-RV also had a higher score on the GADS than those with no GAD. Taken together, a cut-off of 15 was determined to represent a clinically-meaningful cut-point on the self-report GADS scale.
Table D1.

**ROC Curve Analysis to determine the optimal GADS clinical cut-off score**

<table>
<thead>
<tr>
<th>GADS cut-off</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Diagnostic odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>83.3 (35.9-99.6)</td>
<td>78.4 (35.9-99.6%)</td>
<td>3.86</td>
</tr>
<tr>
<td>11</td>
<td>83.3 (35.9-99.6)</td>
<td>82.4 (69.1-91.6)</td>
<td>4.7</td>
</tr>
<tr>
<td>12</td>
<td>83.3 (35.9-99.6)</td>
<td>84.3 (71.4-93.0)</td>
<td>5.3</td>
</tr>
<tr>
<td>13</td>
<td>83.3 (35.9-99.6)</td>
<td>88.2 (76.1-95.6)</td>
<td>7.1</td>
</tr>
<tr>
<td>15*</td>
<td>83.3 (35.9-99.6)</td>
<td>92.2 (81.1-97.8)</td>
<td>10.6</td>
</tr>
<tr>
<td>16</td>
<td>50.0 (11.8-88.2)</td>
<td>94.1 (83.8-98.8)</td>
<td>8.5</td>
</tr>
</tbody>
</table>

*Note. A value was not produced for a GADS cut-off of 14, and is subsequently not reported; GADS = Generalized Anxiety Disorder Scale; CI = Confidence Interval. *preferred clinical cut-off score.
Figure D1. ROC curve produced to identify the optimal clinical cut-off on the GADS, against the SCID-RV.
Appendix E: Conference Presentations


**International Congress of Behavioural Medicine Meeting**, December 2016, Melbourne, Australia. “Lifetime major depression affects self-efficacy and illness perceptions in diabetes by increasing depression and distress” (oral presentation).

**European Association for the Study of Diabetes Annual Meeting**, September 2016, Munich, Germany. “What is the course of depression symptoms in type 2 diabetes? Risk factors and outcomes of 6-year depression trajectories using latent curve growth analysis” (poster displayed by colleague).

American Diabetes Association 76th Annual Congress, June 2016, New Orleans, USA. “What is the course of depression symptoms in type 2 diabetes? Risk factors and outcomes of 6-year depression trajectories using latent curve growth analysis” (late breaking poster presentation).
