Graduate School Form 30
Updated 1/15/2015

PURDUE UNIVERSITY
GRADUATE SCHOOL
Thesis/Dissertation Acceptance

This is to certify that the thesis/dissertation prepared

By Tasneem Khambaty

Entitled

DEPRESSION TREATMENT AND DIABETES RISK: A 9-YEAR FOLLOW-UP STUDY OF THE IMPACT TRIAL

For the degree of Doctor of Philosophy

Is approved by the final examining committee:

Dr. Jesse C. Stewart
Chair

Dr. Adam T. Hirsh

Dr. Catherine E. Mosher

Dr. Christopher M. Callahan

To the best of my knowledge and as understood by the student in the Thesis/Dissertation Agreement, Publication Delay, and Certification Disclaimer (Graduate School Form 32), this thesis/dissertation adheres to the provisions of Purdue University's "Policy of Integrity in Research" and the use of copyright material.

Approved by Major Professor(s): Dr. Jesse C. Stewart

Approved by: Dr. Nicholas J. Grahame 2/10/2015
Head of the Departmental Graduate Program Date

DEPRESSION TREATMENT AND DIABETES RISK:

A 9-YEAR FOLLOW-UP STUDY OF THE IMPACT TRIAL

A Dissertation

Submitted to the Faculty

of

Purdue University

by

Tasneem Khambaty

In Partial Fulfillment of the

Requirements for the Degree

of

Doctor of Philosophy

August 2015

Purdue University

Indianapolis, Indiana

ACKNOWLEDGEMENTS

Thank you, Dr. Jesse Stewart, for your superlative guidance as a mentor, contributions of time and expertise, and assistance at every stage of this process. Thank you sincerely Dr. Christopher Callahan for the use of the IMPACT data for this project. Thank you Joseph G. Kesterson, MA, Regenstrief Institute, Inc., for your help with data management tasks. Finally, my sincere gratitude to my committee members, Dr. Christopher Callahan, Dr. Adam Hirsh, and Dr. Catherine Mosher, for their invaluable expertise and feedback

TABLE OF CONTENTS

Page

Page

Page

Page

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

Khambaty, Tasneem. Ph.D., Purdue University, August 2015. Depression Treatment and Diabetes Risk: A 9-Year Follow-Up Study of the IMPACT Trial. Major Professor: Jesse C. Stewart.

Objectives: To examine the effect of a collaborative care program for late-life depression on risk of diabetes among depressed, older adults.

Method: We conducted a 9-year follow-up study of 160 older, primary care patients with a depressive disorder but without diabetes enrolled at the Indiana sites of the Improving Mood-Promoting Access to Collaborative Treatment (IMPACT) trial.

Results: Surprisingly, the rate of incident diabetes in the collaborative care group (22/80 = 27.5%) was twice the rate observed in the usual care group (11/80 = 13.7%). Cox proportional hazards models adjusted for randomization status (*HR* = 1.94, *p* = .076), demographic factors (*HR* = 1.94, *p* = .075), and additionally for diabetes risk factors (*HR* = 1.73, *p* = .157) indicated that the risk of incident diabetes did not differ between the collaborative care and usual care groups with collaborative care patients remaining at a nonsignificant increased risk.

Conclusions: Our novel findings suggest that depression may not be a casual risk factor for diabetes and that depression treatment may be insufficient to reduce the excess diabetes risk of depressed, older adults.

CHAPTER 1 INTRODUCTION

1.1 Overview

Diabetes is a serious metabolic condition that is highly prevalent worldwide and has substantial consequences for individuals affected by it and for society. Depression is also highly prevalent and is the leading cause of disability worldwide (Pratt & Brody, 2008). Considerable epidemiologic evidence indicates that depression is an independent risk factor for diabetes, with risk ratios similar to traditional diabetes risk factors (Pratt & Brody, 2008). There are also hypothesized behavioral and biological mechanisms that may underlie the depression-to-future-diabetes relationship (Bi et al., 2012; Centers for Disease Control and Prevention, 2011; Mozaffarian et al., 2009). Taken together, these findings suggest that depression may be a causal risk factor for diabetes. Unfortunately, due to the dearth of intervention studies involving depressed patients initially free of diabetes, it is unknown whether depression treatment prevents or delays the onset of diabetes. The proposed study began to address this critical gap in the literature by examining the effect of a collaborative care program for late-life depression on the risk of diabetes among older adults initially free of diabetes. To test the study hypotheses, the present study utilized data from the Improving Mood-Promoting Access to Collaborative Treatment (IMPACT) trial linked with electronic medical record data and Medicare/Medicaid data.

This paper begins with a summary of the significance, prevalence and incidence, pathophysiology, and risk factors of type 2 diabetes. Next, a brief introduction to depressive disorders is provided, followed by a review of the depression-diabetes literature, including both epidemiologic and intervention studies. Then, hypothesized mechanisms that may underlie the depression-to-future-diabetes relationship and the effect of depression treatment on incident diabetes are discussed. Next, the hypotheses and methods of the proposed study are presented, followed by the results obtained from conducting the proposed analyses. In the discussion section, a summary of findings, their fit with the existing literature, and potential interpretations are presented. Limitations of the present study are also discussed, which inform future directions for this research area, the ultimate goal of which is the development of strategies for preventing diabetes among depressed persons.

1.2 Type 2 Diabetes – A Worldwide Epidemic

Diabetes mellitus is a cluster of metabolic diseases usually characterized by deficiencies in insulin secretion, insulin action, or both, ultimately leading to increased glucose concentrations in the blood, known as hyperglycemia (American Diabetes Association, 2010). The two major types of diabetes – Type 1 or insulin dependent and Type 2 or non-insulin dependent – have differing, multifactorial etiologies (Sacks et al., 2011). The unifying feature is that both diseases are characterized by the overproduction and underutilization of glucose (Sacks et al., 2011). Of the two types, type 2 diabetes is the most common in adults, accounting for 90-95% of all diagnosed cases (Centers for Disease Control and Prevention, 2011). Type 2 diabetes is also the primary focus of this

proposal. In the sections below, the term ‘type 2 diabetes’ will be used when referring specifically to this type of diabetes. In contrast, the term ‘diabetes’ will be used to refer to both type 1 or type 2 diabetes together as is commonly done in the literature.

A diagnosis of type 2 diabetes is established when the presence of hyperglycemia can be identified (Sacks et al., 2011). In 1979, and again in 1997, a standardized definition for the diagnosis of diabetes was established by the World Health Organization (WHO) (Sacks et al., 2011). According to their definition, a diagnosis should be given when any one of the following criteria are met on two separate days: (1) a fasting glucose level ≥ 126 mg/dL (7.0 mmol/L), (2) a glucose level two hours after a meal ≥ 200 mg/dL (11.1 mmol/L), or (3) symptoms of diabetes and a casual (i.e., regardless of time of preceding meal) glucose level ≥ 200 mg/dL. Of note, the cut points used in the criteria above were also agreed upon by the International Diabetes Federation and the American Diabetes Association (Sacks et al., 2011). In 2009, these governing bodies proposed that glycosylated hemoglobin (HbA_{1c}) levels ≥ 6.5% should also be used to diagnose type 2 diabetes. HbA_{1c} reflects the average blood glucose concentration over a period of 90-120 days and is therefore considered a more stable estimate than a single fasting or non-fasting glucose measurement (Sacks et al., 2011).

1.2.1 Significance

Diabetes is a chronic, debilitating condition that, within the past few decades, has become a global public health crisis with substantial costs to society (Go et al., 2013). Diabetes is associated with reduced functional status, an elevated risk of complications and other medical conditions, increased health care utilization and costs, and mortality

(Brown, Mangione, Saliba, & Sarkisian, 2003). First, patients with diabetes have reduced functional status and quality of life due to limited mobility, increased pain, and greater dependency on family and friends (American Diabetes Association, 2013; Centers for Disease Control and Prevention, 2011). Another example of reduced functional status particularly relevant to this proposal is the twofold increased risk of depression that is associated with diabetes (Centers for Disease Control and Prevention, 2011). Second, it is well known that diabetes affects several bodily systems. Poorly managed diabetes is the leading cause of kidney failure, lower-limb amputations, and blindness and can also lead to periodontal disease, neuropathy, coma, cerebrovascular disease, and coronary artery disease (Go et al., 2013). Furthermore, individuals with diabetes are more susceptible to other illnesses, such as pneumonia or influenza, and are more likely to have worse prognosis and to die from these illnesses than individuals without diabetes (Centers for Disease Control and Prevention, 2011). Third, diabetes and its complications increase health care utilization and costs. Roughly 15% of hospital discharges in 2009 in the U.S. had diabetes as a listed diagnosis (Go et al., 2013). In 2012, the total costs of diagnosed diabetes were estimated to be $245 billion, of which $176 billion were direct medical costs and $69 billion were indirect costs due to work loss, disability, and premature mortality (American Diabetes Association, 2013). Medical costs for patients with diabetes are also 2.3 times higher than for individuals without diabetes (Centers for Disease Control and Prevention, 2011). Lastly, diabetes is associated with increased mortality. Based on death certificates in 2007, diabetes was the seventh leading cause of

death in the U.S. (Centers for Disease Control and Prevention, 2011). In 2010, 6.8% of deaths worldwide and 15.7% of deaths in North American were attributable to diabetes (Centers for Disease Control and Prevention, 2011).

1.2.2 Prevalence and Incidence

Worldwide, the prevalence of diabetes is 6.6%, a rate that is expected to rise to 7.8% by the year 2030 (International Diabetes Federation, 2009; Stuart & Baune, 2012). In the U.S., the prevalence of diabetes is 8.3%, which amounts to 25.8 million individuals (Centers for Disease Control and Prevention, 2011). Perhaps equally concerning is the fact that 87.3 million individuals are in the pre-diabetic stage and an additional 8.2 million individuals have undiagnosed diabetes (Go et al., 2013). It is also important to note that adults ≥ 65 years have the highest prevalence (26.9%) of diabetes of any age group (Go et al., 2013). With the rate with which the diabetes epidemic is progressing, it is estimated that, in all age, sex, and race/ethnicity groups in the U.S., the total prevalence of diabetes will more than double from 2005 to 2050 (Centers for Disease Control and Prevention, 2011). Moreover, the incidence of diabetes has tripled in the last 20 years. While roughly 600,000 new diabetes cases were diagnosed in 1990, approximately 1.9 million new cases were diagnosed in 2010 among American adults aged 18-79 years (Centers for Disease Control and Prevention, 2012). Taken together, the substantial physical and financial costs and high prevalence and incidence of diabetes underscore the urgent need for approaches to prevent diabetes (American Diabetes Association, 2013).

1.2.3 Pathophysiology

Normal glucose metabolism is primarily regulated by the hormone insulin, produced by the beta-cells in the islet of Langerhans within the pancreas (Stumvoll, Goldstein, & van Haeften, 2005). The primary tissues that insulin targets are liver, fat, and muscle cells (Kahn, 2001b). A feedback loop consisting of the pancreas, liver, and peripheral tissues is responsible for glucose metabolism and glucose-insulin homeostasis (Kahn & Porte, 2003). Within this feedback loop, an interchange occurs between two fundamental processes that results in homeostasis: (1) insulin action – the ability of insulin to act on peripheral tissues to stimulate glucose metabolism and inhibit hepatic glucose output, and (2) insulin secretion – the ability of beta-cells in the pancreas to produce insulin to match glucose output (Stumvoll et al., 2005). An important property of this feedback loop is that normal pancreatic beta-cells can adapt to changes in insulin action or secretion; a decrease in insulin action can lead to a compensatory increase in insulin secretion or vice versa.

In type 2 diabetes, defects occur in both insulin action and secretion (Kahn, 2001a). Defects in insulin action that result in the decreased ability of insulin to act on peripheral tissues to stimulate glucose uptake is known as insulin resistance. Insulin resistance can occur due to several reasons, including defects at the insulin receptor, a decrease in receptor number, and defects at several of the post-receptor steps involved in insulin action (Kahn, 2001a). Once initiated, insulin resistance manifests in skeletal muscles as a reduction in insulin-mediated glucose uptake (Henry, 2003), in the liver as an inadequate suppression of hepatic glucose production, and in the vasculature as abnormal endothelial function and increased production of proinflammatory markers

(Haffner, 2003; Wheatcroft, Williams, Shah, & Kearney, 2003). The ultimate result of insulin resistance is hyperglycemia (Kahn, 2001a).

While nearly 90% of all patients with type 2 diabetes exhibit insulin resistance, its presence alone is not sufficient for type 2 diabetes to develop (Zimmet, Alberti, & Shaw, 2001); defects in insulin secretion as a result of impaired beta-cell function are also necessary (Kahn, 2001b). During the earlier stages of insulin resistance, the pancreas can compensate by increasing insulin secretion. As a result of this hyperinsulinemia, the body metabolizes glucose at normal rates and, therefore, glucose tolerance tests are often normal. This intermediate stage can last from months to years and is known as pre-diabetes. (Boden & Shulman, 2002; Pratley, 2006). In the more advanced pre-diabetic stage, as insulin resistance becomes more severe, high levels of insulin secretion are unable to compensate for the hyperglycemia. As a result of chronically elevated insulin production, individuals become relatively insulin deficient because the size of the beta-cells decreases to nearly 40-60% of what would be considered normal (Weir & Halban, 2001). This decrease in beta-cell mass leads to impaired beta-cell responsiveness to increases in glucose levels to the extent that the body's ability to compensate for changes in insulin resistance becomes absent altogether (Pratley, 2006). At this point, circulating glucose levels are chronically elevated and likely to be identified as such by glucose tolerance tests and fasting or non-fasting glucose tests, leading to a diagnosis of type 2 diabetes (Pratley, 2006).

1.2.4 Risk Factors

As with most chronic diseases, both modifiable and nonmodifiable factors are thought to play an etiological role in the development of type 2 diabetes. Modifiable factors include obesity, physical inactivity, poor diet, smoking, and alcohol consumption, all of which independently predict incident diabetes (Mozaffarian et al., 2009). Of these, obesity has received the greatest attention. In the Nurses' Health Study, women with a body mass index (BMI) of ≥ 35.0 were 38.8 times more likely to develop type 2 diabetes than women with a BMI of < 23.0 (Hu et al., 2001). Second, physical inactivity is positively related to the development of type 2 diabetes. Data from the U.S. National Health and Nutrition Examination Survey (NHANES) revealed that every two hours per day spent watching television was associated with a 14% increase in diabetes risk, while the same amount of time standing or walking was associated with a 12% reduction in risk (Hu, Li, Colditz, Willett, & Manson, 2003). A recent meta-analysis involving 175,938 individuals and 6,428 incident type 2 diabetes cases confirmed this risk, finding that two hours of television per day increased the risk of type 2 diabetes by 20% (Grøntved & Hu, 2011). Third, poor diet has been shown to contribute to the development of diabetes, independent of BMI (Bi et al., 2012; Hu et al., 2001). The Nurses' Health Study found that a higher dietary glycemic load was associated with a 16% increased diabetes risk (Bi et al., 2012; Hu et al., 2001). Additionally, meta-analytic results indicated that a higher consumption of sugar-sweetened beverages was associated with a 26% increased risk of type 2 diabetes (Malik et al., 2010). Fourth, compared to nonsmokers, current smokers have a 45% increased risk of diabetes, a risk that increases in a dose-response fashion with the number of cigarettes smoked (Ainsworth et al., 1993). Lastly, the relationship

between alcohol use and type 2 diabetes exhibits a U-shape, with moderate drinkers at a 30-40% decreased risk than abstainers and heavy drinkers (Koppes, Dekker, Hendriks, Bouter, & Heine, 2005). To put these individual risk factors in perspective, data from the Cardiovascular Health Study found that individuals whose physical activity level and dietary, smoking, and alcohol habits were all in the low-risk group had an 82% lower incidence of type 2 diabetes than all other participants. Absence of obesity lead to a further decrease in risk of disease incidence to 89% (Mozaffarian et al., 2009).

Nonmodifiable factors implicated in the development of type 2 diabetes are demographic factors, hypertension, and genetic factors. Demographic risk factors are older age and race/ethnicity (Centers for Disease Control and Prevention, 2011). Studies show that African Americans, Hispanic/Latino Americans, American Indians, and some Asian Americans, Native Hawaiians, and Pacific Islanders are groups at increased risk for type 2 diabetes compared to Caucasian Americans (Centers for Disease Control and Prevention, 2011). Hypertension is considered a risk factor for prediabetes according to the American Association of Clinical Endocrinologists guidelines (Handelsman et al., 2011), with hypertensive persons thought to be 2.5 times as likely to develop prediabetes and type 2 diabetes than persons with normal blood pressure (Gress, Nieto, Shahar, Wofford, & Brancati, 2000). Moreover, beta-blockers commonly used in the treatment of hypertension appear to increase the risk of type 2 diabetes by 28% (Elliott & Meyer, 2007; Gress et al., 2000). Genetic factors for type 2 diabetes have been a subject of increasing interest in recent years, particularly since the advent of genome-wide association studies (GWAS) (Bi et al., 2012). Much progress has been made in identifying diabetes susceptibility genes, with 38 genetic loci currently confirmed to be

associated with type 2 diabetes by GWAS studies (Bi et al., 2012). Most of the identified diabetes susceptibility genes are thought to affect beta-cell function instead of insulin resistance (Voight et al., 2010).

1.3 Depression as a Potential Risk Factor for Diabetes

In the mid-1980's, researchers began to examine the potential role of psychological factors in the development and progression of type 2 diabetes, given some indication from clinical settings that psychological factors, particularly depressive disorders, were more prevalent among individuals with versus without diabetes (Lloyd et al., 2010). In the sections below, the definition, assessment, and prevalence of depressive disorders is briefly reviewed. Then the depression-diabetes literature, including both epidemiologic and intervention studies is summarized. Lastly, the hypothesized mechanisms that may underlie the depression-to-future-diabetes association and the effect of depression treatment on incident diabetes are discussed.

1.4 Depressive Disorders

Depressive disorders are highly debilitating conditions that affects both an individual's mental and physical health and accounts for more disability than any other disorder worldwide (Pratt & Brody, 2008). These disorders are associated with decreases in quality of life, impairment in social and occupational functioning, and increases in health care costs (Pratt & Brody, 2008). Two types of depressive disorders are major depressive disorder (MDD) and dysthymic disorder (American Psychiatric Association, 2000; Fava & Kendler, 2000). MDD consists of the following four symptom clusters:

affective symptoms (depressed mood and anhedonia), cognitive symptoms (inappropriate guilt, poor concentration, indecisiveness, worthlessness, and recurrent thoughts of death or suicide), behavioral symptoms (psychomotor retardation or agitation), and somatic symptoms (weight loss or gain, sleep disturbances, and fatigue) (Fava & Kendler, 2000). According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR; American Psychiatric Association, 2000), five or more of these symptoms, including depressed mood or anhedonia, must last for at least two weeks for MDD to be diagnosed. Moreover, these symptoms must be the source of significant distress and impairment in one's daily functioning and should not be accounted for by substance use or bereavement (American Psychiatric Association, 2000). Dysthymic disorder is a milder, although more chronic, form of depression in which two or more of the aforementioned symptoms in addition to depressed mood must be present for most of the day for at least 2 years (American Psychiatric Association, 2000).

MDD and dysthymia are diagnosed through structured diagnostic interviews, but they are also commonly assessed using standardized self-report scales. The gold standard diagnostic interview for depression is the Structured Clinical Interview for DSM-IV (SCID; First, Spitzer, Gibbon, & Williams, 2002). The SCID is a semi-structured interview utilized commonly in research settings, which offers psychiatric diagnoses according to DSM-IV criteria by systematically inquiring about the presence or absence of particular symptoms (First et al., 2002). Self-report scales such as the Patient Health Questionnaire-9 (PHQ-9) or the Beck Depression Inventory (BDI) assess depressive

symptom severity. Generally, high scores on these scales are strongly correlated with the presence of depressive disorders (Goldston & Baillie, 2008; Williams Jr, Pignone, Ramirez, & Perez Stellato, 2002).

Worldwide, depressive disorders are responsible for 4.8% of the total burden of disease, with figures increasing to 5.1% and 8.2% in middle and high-income countries respectively (Mathers, Fat, & Boerma, 2008). Moreover, by the year 2030, depressive disorders are thought to become the leading contributor to morbidity (Mathers et al., 2008). MDD is currently the most common of the psychiatric disorders and, among "first-world" countries, the most common of all biomedical disorders (Fava & Kendler, 2000). In the U.S., the lifetime prevalence of MDD is approximately 17% and a 12-month prevalence is 7% (Fava & Kendler, 2000; Kessler, Chiu, Demler, & Walters, 2005). Moreover, data collected in 2005-2006 found that in any 2-week period, 5.4% of Americans aged ≥ 12 years experience clinical depression, a rate that is highest among women, and individuals aged 40-59 years (Pratt & Brody, 2008). With regard to dysthymic disorder, the National Comorbidity Survey Replication reported a lifetime prevalence of 6.4%, and a 12-month prevalence of 1.5% (Kessler et al., 2005).

1.5 Review of the Depression-Diabetes Literature

1.5.1 Epidemiologic Studies

Evidence from early epidemiologic investigations indicated that the prevalence of MDD is higher among individuals with diabetes versus those without this condition (Anderson, Freedland, Clouse, & Lustman, 2001; Lustman, Penckofer, & Clouse, 2007; Talbot & Nouwen, 2000). Systematic reviews have since confirmed that the prevalence

of MDD in patients with diabetes is up to 30%, nearly twofold higher than in patients with other medical illnesses (Ali, Stone, Peters, Davies, & Khunti, 2006; Anderson et al., 2001). While several hypotheses have been posited to explain this high prevalence, the two dominant hypotheses are: (1) depression results from the psychosocial demands associated with the diagnosis and treatment of diabetes, sometimes referred to as the psychological burden hypothesis (Talbot & Nouwen, 2000), and (2) depression is a direct consequence of the pathophysiology or treatment of diabetes, also referred to as a mood disorder due to a medical condition (Talbot & Nouwen, 2000). In 2000, Talbot and Nouwen (2000) conducted a qualitative review of the diabetes-depression literature to gauge the degree of empirical support for these two hypotheses. The researchers included all data published before May 2000 and surprisingly found little evidence to support either hypothesis. Instead, the authors reported that in the majority of prospective studies reviewed, depressive symptomology preceded the onset of type 2 diabetes by several years, which led them to conclude that there is more evidence for depression as a candidate risk factor for type 2 diabetes than a consequence.

The earliest study to document that MDD predicted the development of type 2 diabetes was conducted by Eaton and colleagues (1996). These researchers examined data from 1,715 individuals who were initially free of type 2 diabetes from the Epidemiologic Catchment Area program survey. Participants were followed over 13 years, during which 89 (5.2%) participants developed type 2 diabetes. Logistic models, adjusted for demographic factors and BMI, revealed that MDD predicted the onset of type 2 diabetes. Specifically, individuals with MDD had a more than twofold increased risk of developing type 2 diabetes than nondepressed individuals. This population-based

longitudinal study stimulated future research on the depression-incident diabetes association (Lustman, Penckofer, et al., 2007). In a large community sample of 4,803 adults aged 55 years and older, Campayo et al. (2010) further determined that – even after adjusting for sociodemographic factors, diabetes risk factors, and antidepressant medication use – subclinical or minor depression (*OR* = 1.66), persistent depression (*OR* = 2.09), and untreated depression (*OR* = 1.83) were all associated with greater risk of incident diabetes (either type 1 or type 2).

Utilizing data from the First National Health and Nutrition Examination Epidemiologic Follow-up Study, Carnethon et al. (2003) examined whether the prospective association between depression and diabetes (type 1 or type 2) is mediated by established risk factors for diabetes. Over 16 years, 369 (6%) of the 6,190 adults developed diabetes. The risk of incident diabetes was two times higher among adults depressed at baseline versus those who were not depressed, although only among individuals who had less than a high school education. Moreover, the association between depressive symptoms and incident diabetes was strongest among women. Lastly, 31% of the observed association was explained by BMI, while another 6% was explained by lifestyle behaviors of smoking, alcohol use, and physical inactivity (Carnethon et al., 2003). In a study of 5,201 participants from the Multi-Ethnic Study of Atherosclerosis, Golden et al. (2008) repeatedly measured depressive symptoms and fasting blood glucose over three years. Adjusting for sociodemographic, metabolic, and inflammatory markers, the researchers found that the risk of incident type 2 diabetes was 1.10 times higher for each 5 unit increase in the CES-D scale, suggesting a graded association.

The findings of the aforementioned studies have been further replicated in samples of younger (Brown, Majumdar, Newman, & Johnson, 2005) and older adults (Carnethon et al., 2007), samples of men (Kawakami, Takatsuka, Shimizu, & Ishibashi, 1999) and women (Arroyo et al., 2004; Everson-Rose et al., 2004), and in studies utilizing self-report depression assessments (Kawakami et al., 1999) and diagnostic interviews (Eaton, Armenian, Gallo, Pratt, & Ford, 1996; Mezuk, Eaton, Albrecht, & Golden, 2008). Furthermore, a recent meta-analysis confirms the elevated diabetes risk associated with depression and provides an overall estimate of the magnitude of this prospective association. Mezuk et al. (2008) compiled 20 longitudinal studies to examine (1) diabetes as a predictor of future depression and (2) depression as predictor of future diabetes. The analysis of seven studies exploring the first direction revealed that diabetes was associated with a modest 15% increase in risk of developing depression. The analyses of 13 studies exploring the second direction revealed that depression was associated with a 60% increase in risk of developing type 2 diabetes. Demographic factors were not found to be moderators of this relationship. This meta-analysis suggests that the depression-diabetes relationship is bidirectional, although the magnitude of the depression-to-future-diabetes relationship appears to be stronger than that of the diabetes to depression relationship. To summarize, results of epidemiologic studies suggest that depression is an independent risk factor of type 2 diabetes. Importantly, the risk conferred by depression rivals in magnitude with other known risk factors for the disease, including obesity, smoking, and physical inactivity (Golden et al., 2008; Mezuk et al., 2008).

1.5.2 Treatment Studies

To determine whether depression is a causal risk factor for type 2 diabetes, depression intervention studies are needed. Ideally, these studies would involve adults with depression but not diabetes at baseline. However, there are only a few studies of this type in the literature. Far more intervention studies involve patients with comorbid depression and type 2 diabetes. The aim of these studies has been to determine whether treating depression can improve diabetes prognosis, most commonly indicated by glycemic control (i.e., HbA_{1c} levels) (Katon & Felz-Cornelis, 2010). These studies, although not ideal, can also provide information relevant to this proposal. For instance, if depression treatment among patients with diabetes has a beneficial influence on diabetes markers, these studies would provide indirect support for the notion that depression treatment delivered to depressed patients at risk for diabetes may also influence subclinical diabetes markers or underlying mechanisms (e.g., insulin resistance) and delay or prevent diabetes onset. In the following section, intervention studies involving individuals without and with diabetes at baseline are reviewed.

1.5.2.1 Individuals without Baseline Diabetes

Although not a randomized controlled trial (RCT), a small proof-of-concept study provides initial evidence of a positive effect of depression treatment on subclinical diabetes outcomes. Okamura et al. (2000) compared 20 nondiabetic patients with depression before depression treatment to 13 age-, sex-, and BMI-matched nondiabetic adults without depression. Depressed patients were found to have lower insulin sensitivity than their nondepressed counterparts. Then, during a treatment phase,

depressed patients were given tricyclic or tetracyclic antidepressants and asked to maintain a 1,800–2,200 kcal per day diet and avoid aerobic exercise. Okamura et al. compared their pre- and post-treatment oral glucose tolerance tests and found that there was significant improvement in insulin sensitivity after treatment, with no concurrent changes in the BMI or fasting blood glucose. These results suggest that depression treatment may decrease the risk of diabetes by improving insulin sensitivity.

In a double-blind RCT (Weber-Hamann, Gilles, Lederbogen, Heuser, & Deuschle, 2006), 80 inpatients with MDD but not diabetes were randomized to either paroxetine (a selective serotonin reuptake inhibitor; SSRI) or amitriptyline (a tricyclic antidepressant). Over a 5-week period, insulin sensitivity improved only among patients who achieved depression remission following treatment with either antidepressant. Improvement in insulin sensitivity was again not accounted for by changes in BMI. A subsequent investigation by the same authors found similar results. In that study, 51 inpatients with MDD but not diabetes were given either mirtazapine (a tetracyclic antidepressant) or venlafaxine (a dual noradrenergic and serotonergic reuptake inhibitor) (Weber-Hamann et al., 2008). Over the 4-week treatment period, depression remission was associated with a significant improvement in insulin sensitivity, with a nonsignificant trend towards a more pronounced effect of mirtazapine than venlafaxine. However, there was no effect of antidepressants on insulin sensitivity in the absence of depression remission, suggesting that the observed effect was depression dependent and not due to the direct physiologic effects of the medications.

In contrast, another study reported a null effect of depression treatment on insulin sensitivity. Kauffman et al. (2005) enrolled 14 depressed and 18 nondepressed women

aged 18-45 years. All depressed women were given citalopram (a SSRI), and the nondepressed women were randomly assigned to citalopram or no treatment. Before treatment, no differences in insulin sensitivity were found between depressed and nondepressed women. After 8 weeks of treatment, no differences were detected in oral glucose tolerance tests between the three groups, indicating no improvement in insulin sensitivity. The fact that the depressed women were euglycemic at baseline may partly explain the lack of group differences, as it is possible that there was limited margin for improvement in insulin sensitivity.

To summarize, there are few studies that evaluate the effect of depression treatment on diabetes-related outcomes among individuals initially free of diabetes. The available data suggests that depression treatment may improve insulin sensitivity and, therefore, provides preliminary support for the notion that depression treatment may prevent or delay the onset of type 2 diabetes. Of note, the effect on insulin sensitivity may be depression dependent, as remission appears to be required. However, given that the existing trials are small and lacking in methodological rigor (e.g., lack of randomization and absence of a control group), there is a need for well-designed intervention studies evaluating the effect of depression treatment on incident diabetes among depressed patients without diabetes at baseline.

1.5.2.2 Individuals with Baseline Diabetes

Among individuals with comorbid depression and diabetes, research has primarily examined whether depression interventions reduce depressive symptoms and only secondarily examined whether these interventions also improve diabetes outcomes.

Because the secondary question is more relevant to this proposal, I review the existing studies utilizing pharmacological, psychological, or collaborative care interventions below, with a focus on diabetes outcomes.

1.5.2.2.1 Pharmacologic Interventions

Lustman et al. (1997) conducted one of the earliest trials in this area, enrolling 68 patients with type 1 or type 2 diabetes, of which 28 individuals also had MDD. Participants were randomized to an 8-week regimen of either nortriptyline (a tricyclic antidepressant) or placebo. Analyses revealed that, compared to placebo, nortriptyline significantly improved depression symptoms but not HbA_{1c} levels. In subsequent path analyses, the authors found that while the direct effect of nortriptyline was to worsen HbA_{1c} levels, the effect of depression remission was to improve glycemic control. Given the detrimental effects of tricyclic antidepressants, in a subsequent study, the same researchers investigated the effects of fluoxetine (a SSRI) on glycemic control among 60 diabetic patients (type 1 or type 2) with MDD (Lustman, Freedland, Griffith, & Clouse, 2000). After an 8-week treatment period, participants given antidepressant medication compared to placebo showed a trend toward greater reduction in HbA_{1c} levels. Of note, neither changes in weight loss nor depression were responsible for this effect. Although providing only modest evidence that pharmacologic depression treatment influences diabetes outcomes, these studies suggest that the effect of antidepressant medications on diabetes markers was not uniform (Lustman, Williams, Sayuk, Nix, & Clouse, 2007). Specifically, it appeared that while older tricyclic antidepressants had hyperglycemic effects, newer SSRIs had hypoglycemic or null effects.

Longer term studies that examine the efficacy of continuing antidepressant medication to prevent depression relapse more clearly demonstrate that improvement in depression leads to better glycemic control. For instance, in a double-blind RCT, 351 patients with comorbid MDD and type 2 diabetes were given sertraline during a 16-week treatment phase (Lustman et al., 2006). After this phase, the 152 patients who recovered from depression continued to a maintenance phase in which they were randomized to treatment with sertraline at a remission dose or placebo for the next 52 weeks or until depression recurred (Lustman et al., 2006). HbA_{1c} levels were reduced not only in the treatment phase, but also the maintenance phase compared to baseline, indicating a positive effect of depression treatment on glycemic control. A subsequent smaller study confirmed these findings and further attributed improvements in glycemic control directly to depression improvement (Lustman, Penckofer, et al., 2007). These longer term studies lend further support to the notion that depression remission may be required for there to be salutary effects on diabetes markers.

1.5.2.2.2 Psychological Interventions

Several studies have examined the effects of psychological interventions on diabetes outcomes, with the main advantage of removing any potential for direct medication effects. As an example, one study assessed the influence of cognitive behavioral therapy (CBT) on depression and HbA_{1c} levels over a 10-week treatment phase and an additional 6-month follow-up period (Lustman, Griffith, Freedland, Kissel, & Clouse, 1998). The study involved a comparison of an individual CBT program plus diabetes education to diabetes education alone. While no statistically significant

difference was observed in HbA_{1c} levels between groups at post-treatment, lower HbA_{1c} levels were observed in the CBT group at the 6-month follow-up. Regarding the lag in glycemic control improvement, the authors reasoned that, because HbA_{1c} is a "weighted" measure that averages blood glucose levels over the preceding 90-120 days, the 6-month HbA_{1c} value, but not the post-treatment value measured directly after the treatment period would reflect improvement (Lustman et al., 1998). Although another study utilizing a nurse-administered minimal CBT program (4 sessions) corroborated the above findings (Lamers, Jonkers, Bosma, Knottnerus, & van Eijk, 2011), other investigations using web-based CBT (van Bastelaar, Pouwer, Cuijpers, Riper, & Snoek, 2011) or telephone CBT (Piette et al., 2011) demonstrated null results.

1.5.2.2.3 Collaborative Care Interventions

A collaborative care intervention is a health services model designed to deliver evidence-based depression treatment in primary care settings (Katon & Felz-Cornelis, 2010; Van der Feltz-Cornelis et al., 2010). A collaborative care intervention generally consists of the following components: (1) a team approach to care in which depression specialists work with primary care physicians to deliver depression care, (2) the use of brief assessments to monitor symptoms, and (3) stepped care approaches, which involve complementing or changing initial pharmacologic or psychological treatment based on the persistence of symptoms (Katon & Felz-Cornelis, 2010; Katon & Seelig, 2008). At least four collaborative care interventions trials have been conducted among depressed patients with diabetes (Ell et al., 2010; Katon & Felz-Cornelis, 2010; Katon et al., 2004; Williams, Katon, et al., 2004). One such trial conducted by Williams et al. (2004) is a

good example, as they examined data that will also be utilized in the present study. The researchers conducted a preplanned subgroup analysis involving the 417 participants of the IMPACT trial who had diabetes at baseline. Along with the 1,384 IMPACT participants without diabetes, these individuals were randomized to the IMPACT intervention, a 12-month collaborative care intervention for late-life depression, or to usual care. Patients in the intervention group received a stepped care program consisting of antidepressant medication and/or problem solving therapy, while usual care patients received notification, along with their primary care physician, that they met criteria for a depressive disorder and were encouraged to follow-up regarding their symptoms. Analyses revealed significant decreases in depressive symptoms in the collaborative care versus usual care group, but no difference in HbA_{1c} levels. Importantly, the three other collaborative care trials similarly failed to detect an effect of collaborative depression care on glycemic control. One explanation for these null results offered by Williams et al. (2004) was that, because the patients exhibited good glycemic control at baseline, there may have been a limited margin to detect further improvements. In addition, a lack of recovery from depression in the intervention arm may also be responsible for the null effects on diabetes outcomes. For example, in the Pathways study (Katon et al., 2004), roughly 45% of intervention patients had significant depressive symptoms at the end of the treatment period. Lastly, if improvement in glycemic control lags behind improvement in depressive symptoms, assessment of glycemic control immediately after treatment may have been premature, yielding no differences.

To date, one meta-analysis has aggregated data from existing clinical trials. Van der Feltz-Cornelis et al. (2010) identified 14 trials, of which six utilized pharmacologic

interventions, five utilized psychological interventions, and three utilized collaborative care interventions. The standardized effect sizes of the pharmacologic trials, of which all but one evaluated the effect of SSRIs, was moderate for depressive symptoms (d = -0.61) and small for glycemic control (d = -0.38). The standardized effect size of the psychological interventions was moderate-to-large for both depressive symptoms (d = -0.64) and glycemic control (d = -0.48). With regard to the collaborative care trials (Ell et al., 2010; Williams, Katon, et al., 2004), the authors only provided a pooled effect size for a combined outcome of depression and glycemic control (d = -0.29) (Katon & Felz-Cornelis, 2010). However, given that none of these trials reported significant improvement in glycemic control, this pooled effect size likely reflects improvement only in depressive symptoms in the collaborative care arm compared to the usual care arm.

In summary of intervention studies involving patients with comorbid depression and diabetes, some but not all studies indicate that depression treatment improves both depression and diabetes outcomes. These studies further suggest that depression remission may be a necessary component if improvement is to occur in diabetes outcomes. However, in terms of determining whether depression may be a potentially causal risk factor for diabetes, these studies are not ideal due to their choice of participants (patients with diabetes at baseline). Nonetheless, these studies provide indirect support for the notion that depression treatment delivered to depressed patients at risk for diabetes may also influence subclinical diabetes markers or underlying mechanisms (e.g., insulin resistance) and delay or prevent diabetes onset.

1.6 Potential Mechanisms Underlying the Depression-Diabetes Relationship

Several behavioral and biological mechanisms have been proposed to explain the prospective association between depression and diabetes (see Figure 1), although they remain poorly understood. It is known, however, that these candidate mechanisms are interrelated and discussion of one often includes reference to others (Stuart & Baune, 2012). These mechanisms are reviewed in the next two sections. Furthermore, several of the same mechanisms are also hypothesized to mediate the effect of depression treatment on diabetes outcomes. The third section below discusses the available mechanistic findings from intervention studies.

1.6.1 Behavioral Mechanisms

Depressed patients exhibit poor health behaviors that can increase diabetes risk (Golden et al., 2008; Ismail, 2010). Research shows that depressed patients are more likely to have deleterious dietary and physical activity behaviors (Golden et al., 2008; Ismail, 2010; Marcus, Wing, Guare, Blair, & Jawad, 1992; Roose et al., 2006), resulting in greater caloric intake (Golden, 2007; Golden et al., 2004) and a sedentary lifestyle (Carnethon et al., 2007; Carnethon et al., 2003; Everson-Rose et al., 2004). Depressed patients are also more likely to be noncompliant with medication, exercise, and diet recommendations, which can prolong depressive symptoms and further promote overeating and a sedentary behavior (Ismail, 2010). All of these factors have been shown to contribute to obesity, which is a strong risk factor for type 2 diabetes (Ismail, 2010). Moreover, physical inactivity decreases insulin sensitivity and is considered a risk factor for insulin resistance independent of obesity (Wagner, Allen, Swalley, Melkus, &

Whittemore, 2009; Weber-Hamann et al., 2006). Furthermore, depressed patients are twice as likely to engage in smoking as non-depressed patients (Lin et al., 2004; Strine et al., 2008). In turn, smoking is a risk factor for diabetes via its association with central obesity, increased inflammation, and beta-cell function damage (Canoy et al., 2005; Chang, 2012; Morrow et al., 1995; Spector & Blake).

1.6.2 Biological Mechanisms

Depression may activate several interrelated biological systems that can result in the development of insulin resistance and type 2 diabetes. These systems include the hypothalamic-pituitary-adrenal (HPA) axis, the sympathetic nervous system, and the innate immune system (Ismail, 2010). Depression is associated with HPA axis hyperactivation, as evidenced by elevated free, unbound cortisol levels in the plasma, increased 24-hour urinary free cortisol secretion, and elevated corticotropin releasing hormone levels in cerebrospinal fluid among depressed patients compared to controls (Fountoulakis, Gonda, Rihmer, Fokas, & Iacovides, 2008; Ismail, 2010; Otte et al., 2004; Rustad, Musselman, & Nemeroff, 2011; Stewart, 2008; Vreeburg et al., 2009). While a temporary HPA hyperactivation initiates a cascade of responses ending with the release of cortisol into the blood to help address the stressor, chronically high cortisol levels (a) activate the body's innate inflammatory response, (b) contribute to increased visceral fat and central adiposity, and (c) activate the sympathetic nervous system resulting in the further increase in inflammatory markers and the release of catecholamines epinephrine and norepinephrine (Ismail, 2010; Roose et al., 2006). The collective metabolic effect of increased cortisol levels is to stimulate glucose production, decrease insulin secretion

from beta-cells, and decrease insulin sensitivity, all of which are implicated in the pathogenesis of type 2 diabetes (Knol et al., 2006; Rustad et al., 2011; Stewart, 2008).

The finding that depression is associated with immune system activation and increased synthesis of inflammatory markers, including acute phase proteins (e.g., C-reactive protein) and proinflammatory cytokines (e.g., interleukin-6), has been found in both human and animal studies (Howren, Lamkin, & Suls, 2009; Nouwen et al., 2011). Additionally, the presence of obesity among depressed patients also leads to proinflammatory cytokine production from adipocytes and macrophages accumulated in fat tissue (Ismail, 2010). These inflammatory markers inhibit insulin's intracellular signaling cascade, ultimately decreasing insulin sensitivity and contributing to the development of type 2 diabetes (Ismail, 2010; Stuart & Baune, 2012). Moreover, a proinflammatory state within the liver and skeletal muscle, which are the primary tissues responsible for the maintenance of glucose homeostasis in response to insulin, can lead to insulin resistance within these tissues and result in pancreatic beta-cell apoptosis that is characteristic of type 2 diabetes (Stuart & Baune, 2012).

1.6.3 Treatment Mechanisms

Some but not all intervention studies demonstrate that depression treatment improves insulin sensitivity among depressed patients without diabetes and glycemic control among depressed patients with diabetes. With regard to the positive effect of depression treatment on diabetes outcomes, researchers hypothesize that the treatment-related reductions in depressive symptoms may result in improvement in several of the

behavioral and biological mediators depicted in Figure 1, which in turn could delay or prevent the onset of insulin resistance and type 2 diabetes.

A number of intervention studies have also explored candidate mechanisms underlying observed treatment effects. In terms of behavioral mediators, body weight/composition has thus far received the most attention. On the one hand, Lustman et al. (2007) found that improvements in glycemic control over the treatment period were due to improvement in both body composition and depressive symptoms. On the other hand, other studies indicate that the effect of depression treatment on insulin sensitivity among nondiabetic individuals and on glycemic control among diabetic individuals was unrelated to changes in BMI or body composition (Lustman et al., 2000; Lustman et al., 1997; Okamura et al., 2000; Weber-Hamann et al., 2006; Weber-Hamann et al., 2008). A second behavioral mediator examined in diabetes trials has been diabetes self-care. The path analysis conducted by Lustman et al. (1997) and the maintenance trial by the same researchers (Lustman et al., 2007) found that the effect of antidepressant medication on glycemic control was not due to better compliance with self-monitoring of blood glucose or other types of diabetes self-care. Other behavioral mediators, such as physical activity could also underlie the effect of depression treatment on incident diabetes, but have not been assessed in treatment trials thus far. In terms of biological mediators, studies involving individuals initially free of diabetes (Okamura et al., 2000; Weber-Hamann et al., 2006; Weber-Hamann et al., 2008) suggest that depression treatment may delay or prevent type 2 diabetes by improving insulin sensitivity. Weber-Hamann et al. (2006) also found a decline in cortisol levels after depression treatment, which could lead to improved insulin sensitivity. However, decreased cortisol levels were found only among

individuals who received one type of antidepressant medication (amitriptyline) but not another (paroxetine). Other biological mediators, such as decreased systemic inflammation or sympathetic nervous system activation could also result in decreased risk of type 2 diabetes, but have not been assessed in treatment trials thus far. In short, this research remains incomplete and is far from conclusive. Furthermore, very few studies have conducted tests of statistical mediation. Such tests in future investigations may provide valuable data and eventually allow for the targeting of these specific mechanisms to prevent type 2 diabetes among depressed individuals.

1.7 The Present Study

Beginning with the earliest study by Eaton et al. (1996), data from prospective epidemiologic studies provide convincing evidence that depression is an independent risk factor for type 2 diabetes. However, intervention studies involving depressed adults initially free of diabetes seeking to test whether depression is a causal risk factor for type 2 diabetes are scarce and contain important methodological flaws. The few available studies provide preliminary evidence that depression treatment improves insulin sensitivity and suggest that depression remission may be required for there to be any influence on diabetes markers. More intervention studies have been conducted among depressed patients with diabetes, although these types of studies cannot address whether depression plays a role in the development type 2 diabetes. Nonetheless, this indirect evidence suggests that depression treatment may be effective in addressing the hyperglycemia present in diabetic patients, although not unequivocally. To summarize,

given the lack of well-designed intervention trials involving depressed patients without diabetes, it remains unknown whether evidence-based depression treatment prevents or delays the onset of type 2 diabetes.

The present study began to address this critical gap in the literature by examining the effect of a collaborative care program for late-life depression on the risk of diabetes among older adults initially free of diabetes. The specific hypotheses of this study were:

Hypothesis #1: Depressed patients randomized to collaborative depression care have a lower incidence of type 2 diabetes than depressed patients randomized to usual care.

Hypothesis #2: Change in depressive symptoms during the trial mediates the hypothesized beneficial effect of collaborative depression care on incident diabetes.

Hypothesis #3: Antidepressant treatment received during the trial mediates the hypothesized beneficial effect of collaborative depression care on incident diabetes.

Hypothesis #4: Psychotherapy received during the trial mediates the hypothesized beneficial effect of collaborative depression care on incident diabetes.

To test these hypotheses, a 9-year follow-up study of the Improving Mood-Promoting Access to Collaborative Treatment (IMPACT) trial was conducted. The IMPACT trial was a multisite RCT examining the effectiveness of a collaborative care program for late-life depression. Briefly, 1,801 older, depressed primary care patients were randomly assigned to the IMPACT intervention, a 12-month collaborative care program that included antidepressants and/or psychotherapy, or to usual care. The IMPACT intervention was found to be more effective than usual care in reducing depressive symptoms; 45% of the IMPACT patients, versus 19% of the usual care

patients, achieved a 50% reduction in SCL-20 score at 12-month follow-up (Unützer, Katon, et al., 2002). The present study utilized data from the 235 participants enrolled from the Indiana sites of the IMPACT trial, linked with electronic medical record data and Medicare/Medicaid data to provide the 9 years of follow-up. This combination of data is unique and addresses some of the limitations of previous studies, including small sample sizes and the absence of a control group. Demonstrating that depression treatment reduces the risk of type 2 diabetes would identify depression as a modifiable risk factor for diabetes and suggest that depression treatment should be included in diabetes prevention efforts.

CHAPTER 2 METHOD

2.1 Participants

The IMPACT trial was conducted from 1999 to 2002 at seven study sites across five states (Unützer, Katon, et al., 2002). Participants were from 18 primary care clinics representing 8 diverse health care organizations. The study protocol was reviewed and approved by institutional review boards at all sites as well as the study coordinating center. All participants provided written informed consent.

To recruit a sample from the target population of depressed, older adults, a two-pronged strategy was used (Unützer, Katon, et al., 2002). The first strategy was to systematically screen (either in person or over the telephone) English speaking, older adults attending the participating primary care clinics using a two-item depression screener adapted from the PRIME-MD (Spitzer et al., 1994). The second strategy was to distribute promotions for the study at the participating clinics and accept referrals from the primary care physicians, clinic staff, or the patients themselves. Recruitment occurred from July 1999 to August 2001, with a total of 32,908 individuals approached. The aforementioned recruitment strategies yielded 2,638 individuals with a positive depression screen and an additional 1,626 referred individuals. These potential participants subsequently underwent a 60-minute eligibility interview, consisting

primarily of the SCID diagnostic interview for depression (First et al., 2002). Eligibility criteria were minimal. Inclusion criteria were (a) a positive SCID diagnosis for MDD or dysthymia, (b) age ≥ 60 years, and (c) intent to use one of the participating clinics as the main source of general medical care over the course of the trial (i.e., the next 12 months). Exclusion criteria were (a) a current drinking problem (Mayfield, McLeod, & Hall, 1974), (b) a history of bipolar disorder or psychosis, (c) severe cognitive impairment (Callahan, Unverzagt, Hui, Perkins, & Hendrie, 2002), (d) acute risk of suicide, and (e) ongoing treatment with a psychiatrist. Based on these eligibility criteria, 2,102 eligible individuals were identified, of whom 1,801 enrolled in the trial.

The present study was a 9-year follow-up of the 235 IMPACT participants enrolled from the Indiana sites of the trial (see Figure 2 for a flowchart of participants from the Indiana sites). Follow-up data was obtained from the Regenstrief Medical Record System (RMRS; McDonald, Tierney, Overhage, Martin, & Wilson, 1992), merged with claims data from the Center for Medicare and Medicaid Services (CMS). The RMRS, a local electronic medical record system, is one of the largest and longest operating systems for capturing, maintaining, and retrieving routine and research-oriented clinical data, including registration information, nursing assessments, orders, vital signs, laboratory and prescription medication data, and diagnostic and procedural codes (McDonald et al., 1992). To provide this data, the RMRS links five health care systems, 11 acute care hospitals, 13 homeless care sites, and roughly 100 clinics/offices in the Indianapolis area (Overhage, McDonald, & Suico, 2000). Additionally, death certificate data that includes date and cause of death is routinely obtained from Indiana State Department of Health and incorporated into the RMRS. CMS (www.cms.gov) is a federal

agency responsible for Medicare and Medicaid, two health insurance programs for adults aged ≥ 65 years and for low income families, respectively. CMS enters data regarding insurance claims made by Medicare and Medicaid beneficiaries for hospitalization expenses, outpatient medical care, and prescription drugs into an analyzable database (Hennessy, Leonard, Palumbo, Newcomb, & Bilker, 2007). For the present study, the RMRS provided data for years 1978-2009 and CMS for years 1999-2009. The IUPUI Institutional Review Board and the CMS Privacy Board approved the use of RMRS and CMS follow-up data for the Indiana participants of the IMPACT trial. A waiver of consent was obtained to link RMRS and Medicare/Medicaid data.

2.2 Treatment Groups

After completing the structured baseline interview, participants were randomly assigned to one of two groups – either the 12-month IMPACT collaborative care program or usual care (Unützer, Katon, et al., 2002). Randomization was stratified by type of recruitment (screening or referral) and by clinic. Within each stratum, a random number sequence developed using a computer random number generator at the coordinating center was used to assign participants to the two groups. A set of numbered, sealed envelopes held assignment information in each clinic. When a new patient was enrolled, the next sequential envelop was opened.

2.2.1 IMPACT intervention

Participants in the IMPACT intervention group initially received a 20-minute education videotape and a booklet about late-life depression, and they were encouraged

to schedule an initial treatment visit with a depression clinical specialist (DCS) at their regular primary care clinic (Unützer, Katon, et al., 2002). DCSs were either nurses or psychologists, trained according to the IMPACT intervention manual (Unutzer, 1999). At the initial treatment visit, DCSs conducted an intake interview, during which they assessed patients' medical and psychosocial history, reviewed psychoeducational materials, and discussed patients' preferences for depression treatment – i.e., antidepressant medication or psychotherapy. New participants were discussed during weekly team meetings attended by the DCS, a supervising team psychiatrist, and a liaison primary care physician. Incorporating patient preferences and feedback from the team meetings, the DCS established a depression treatment plan in line with the IMPACT treatment algorithm (Unützer, Katon, et al., 2002). This algorithm recommended a sequence of treatment steps and was based on depression treatment guidelines that were current when the trial was designed (Agency for Health Care Policy and Research Depression Guideline Panel, 1993; Lebowitz et al., 1997). Step 1 of the algorithm recommended that patients start an antidepressant (usually a SSRI) or a course of Problem Solving Treatment in Primary Care (PST-PC; Hegel, Barrett, Oxman, Mynors-Wallis, & Gath, 1999). PST-PC, a 6-8 session, structured cognitive-behavioral therapy for depression, was delivered by the DCSs in the primary care setting. Of the participants already receiving antidepressant medications when they entered the study but who had not achieved remission were encouraged to augment their treatment with a trial of PST-PC, whereas nonresponders were encouraged to switch to a different medication, or to PST-PC. Individuals who did not respond in 8-12 weeks of the Step 1 treatment plan proceeded to Step 2 of the algorithm, which consisted of further augmenting current

antidepressant medication with another medication, switching to a different antidepressant medication, switching from medication to PST-PC, or from PST-PC to medication. DCSs also discussed these patients during the weekly team meetings, and the team psychiatrist met with those patients who presented treatment challenges in the patient's primary care clinic. If after 10 weeks of the Step 2 treatment plan participants still had not achieved remission, they were again discussed during the treatment team meetings. For these individuals, other treatments were considered, including further medication changes or psychotherapy, hospitalization, or electroconvulsive therapy. Of note, while the IMPACT algorithm provided guidance in implementing a treatment plan, the patient and their primary care provider together made the final treatment choices.

During the 12-month IMPACT intervention period, patients' symptoms were monitored using the PHQ-9 (Kroenke, Spitzer, & Williams, 2001) and a web-based clinical information system (Unützer, Choi, Cook, & Oishi, 2002). DCSs contacted patients at least every other week to monitor symptoms, encourage them to schedule pleasant life events and adhere to antidepressant regimens, and refer them to additional health or social services as needed. Patients who achieved a $\geq$ 50% reduction in their PHQ-9 score and exhibited fewer than 3 of 9 symptoms were considered to be in remission. For these patients, DCSs developed a relapse prevention plan and then contacted them to follow-up every month thereafter until the end of the intervention period.

2.2.2 Usual Care

Patients assigned to the usual care group were notified that they met study criteria for a depressive disorder and were encouraged to follow-up with their primary care provider, who also received notification of their patient's diagnosis and treatment group assignment (Unützer et al., 2001). Patients in this group were not restricted in the type of care they could receive, including any primary care or specialty mental health treatments. They were then observed over the intervention period (Unützer et al., 2001).

2.3 Measures

2.3.1 Baseline Diabetes

Because this study focused on the influence of depression treatment on incident diabetes, participants with diabetes at baseline (1999-2001) were excluded from all analyses. To identify these participants, a Regenstrief data manager first queried the RMRS and CMS databases to generate data for each diabetes variable that would be considered for inclusion in the baseline diabetes definition (see Table 1). These variables were: (1a) diabetes diagnoses – ICD-9 hospital, admitting, primary care, or clinic billing code of 250; (1b) diabetes diagnoses – the presence of a diabetes diagnosis in the RMRS text fields; (2) diabetes complications – the presence of diabetes-related nephropathy, enteropathy, foot ulcer, lipodystrophy, retinopathy, or skin ulcer in the RMRS text fields; (3a) diabetes laboratory values – a fasting glucose value $\geq$ 126 mg/dL (Sacks et al., 2011); (3b) diabetes laboratory values – an HbA_{1c} value $\geq$ 8.5%; (4a) diabetes medications – prescription for insulin; (4b) diabetes medications – prescription for oral hypoglycemic medications; and (5) self-reported diabetes – participants answering 'yes'

to the IMPACT baseline interview question, “Has a doctor or another health care worker diagnosed you with or treated you for high blood sugar or diabetes in the past 3 years?” (Unützer, Choi, et al., 2002). Of note, a cut point of $\geq 8.5\%$ was chosen for HbA_{1c} rather than the originally proposed cut point of $\geq 6.5\%$ because recently published guidelines recommend the use of a higher cut point (between 8-9%) for diabetes diagnosis among older adults who have comorbid conditions, such as those participating in the IMPACT trial (American Geriatrics Society Expert Panel on the Care of Older Adults with Diabetes Mellitus, 2013). The midpoint of the recommended range (8.5%) was chosen for this study.

Next, the data manager generated yes/no variables and their corresponding dates for each diabetes variable, except (3a) fasting glucose and (3b) HbA_{1c}, for which the data manager obtained all values in RMRS during the baseline period (1978-2001). This resulted in two separate datasets for fasting glucose and HbA_{1c} values, with multiple rows per person. To aggregate this laboratory data, the value closest to participants’ IMPACT enrollment date that was at or above the cut point was chosen for each participant and coded as ‘1’ (yes). If a participant did not have any values that were at or above the cut point, a code of ‘0’ (no) was given.

Once all yes/no diabetes variables were generated, frequencies were examined and compared to expected prevalence rates in the population to ensure that the query produced adequate capture of baseline diabetes. When systematically missing data were identified during this initial examination (e.g., no fasting glucose data for the years 1994-1997), the data sources were queried a second time using a more comprehensive set of

dictionary terms. Once all data irregularities were resolved, new frequencies were examined. Table 1 presents the baseline diabetes variables listed above and their respective frequencies.

Considering all aforementioned baseline diabetes variables, the primary definition of baseline diabetes was determined to be the presence of a diabetes diagnosis (ICD-9 hospital, admitting, primary care, or clinic billing code of 250) and any one of the following before participants' IMPACT enrollment date: (1) a fasting glucose value ≥ 126 mg/dL; (2) an HbA_{1c} value ≥ 8.5%; or (3) a prescription for diabetes medication (insulin or oral hypoglycemic medication). Because this definition required a diabetes diagnosis in addition to a positive laboratory value or medication use, it was thought to provide the best balance of sensitivity and specificity. The other diabetes variables were not utilized due to (a) worse data capture leading to lower than expected prevalence rates, (b) inconsistent use in prior studies, and/or (c) poor overlap with other diabetes variables. The resultant baseline diabetes variable was a 0/1 variable, where '1' indicated the presence of diabetes prior to participants' IMPACT enrollment date. Participants with a '1' on this variable (n = 75) were excluded from all analyses.

2.3.2 Incident Diabetes

To identify the participants who developed diabetes during the follow-up period, RMRS and CMS databases were again queried to obtain the following incident diabetes variables (see Table 2): (1a) diabetes diagnoses – ICD-9 hospital, admitting, primary care, or clinic billing code of 250; (1b) diabetes diagnoses – the presence of a diabetes diagnosis in the RMRS text fields; (2) diabetes complications – the presence of diabetes-

related nephropathy, enteropathy, foot ulcer, lipodystrophy, retinopathy, or skin ulcer in the RMRS text fields; (3a) diabetes laboratory values – a fasting glucose value ≥ 126 mg/dL (Sacks et al., 2011); (3b) diabetes laboratory values – an HbA_{1c} value ≥ 8.5%; (4a) diabetes medications – prescription for insulin; (4b) diabetes medications – prescription for oral hypoglycemic medications.

Similar to the baseline diabetes variables, the data manager (who was blind to treatment assignment) generated yes/no incident diabetes variables and their corresponding dates, except for (3a) fasting glucose, and (3b) HbA_{1c}, for which the data manager obtained all values in RMRS during the follow-up period. Again, this resulted in two separate datasets for fasting glucose and HbA_{1c} values, with multiple rows per person. To aggregate this data, the earliest value during the follow-up period that was at or above the cut point was chosen for each participant and coded as '1' (yes). If a participant did not have any values that were at or above the cut point, the earliest value during the follow-up was chosen and coded as '0' (no). Once all yes/no variables were generated, frequencies were examined and compared to expected incidence rates in the population. Table 2 presents the incident diabetes variables listed above and their respective frequencies.

Consistent with the baseline definition, the primary outcome was defined as the first occurrence of a diabetes diagnosis (ICD-9 hospital, admitting, primary care, or clinic billing code of 250) and any one of the following during the period between participants' IMPACT enrollment and December 31, 2009: (1) a fasting glucose value ≥ 126 mg/dL; (2) an HbA_{1c} value ≥ 8.5%; or (3) a prescription for diabetes medication (insulin or oral hypoglycemic medication). This resulted in a 0/1 variable, where '1' indicated incident

diabetes. To code the date associated with an incident diabetes event, first the earliest date among (1), (2) and (3) was chosen and compared to the date of a participant's ICD-9 diabetes diagnosis. Then, the latest date of the two was chosen because the incident diabetes definition required both components to be present. Of note, participants were followed until December 31, 2009, because CMS data were available locally up until this date. The total follow-up time was between 8.5 and 10.5 years.

Both RMRS and CMS data are used extensively in epidemiologic, clinical, health services, and policy research and are valid data sources (Hennessy et al., 2007; Platt & Ommaya, 2005; Ray, 1997). For example, the validity of vital status in the RMRS and CMS appears to be very good; 97% of individuals have the same vital status in the two databases (Hennessy et al., 2007). Moreover, CMS data demonstrate infrequent obvious diagnostic miscoding, stable counts of prescription claims over time, and a high proportion of valid drug codes on prescription records (Hennessy et al., 2007). Lastly, a recent study examining the validity of billing and hospital discharge diagnoses in a claims database similar to CMS revealed that sensitivity for diabetes diagnosis was acceptable (64%) and specificity was excellent (97%) (Wilchesky, Tamblyn, & Huang, 2004).

2.3.3 Other Variables

During the IMPACT baseline interview, patients were asked by trained lay interviewers about demographic information (age, sex, race/ethnicity) and if they had been diagnosed or treated for any of 10 common chronic medical problems in the preceding 3 years, including diabetes and hypertension (Unützer et al., 2001). Data

regarding baseline smoking status and BMI were obtained through RMRS. Several indicators of smoking status were obtained, including any smoking diagnoses, yes/no markers for current smoking status, and packs-per-day information. If any of these indicators was positive, the participant received a code of '1' (yes) on smoking status; otherwise, the participant received a code of '0' (no). Height and weight information was also obtained from RMRS. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2).

Depression variables assessed during the baseline interview were depressive symptom severity and participants' use of antidepressants in the preceding 3 months. Depression symptom severity was assessed using the 20 depression items of the Symptom Checklist-90 (SCL-20; Derogatis, Lipman, & Covi, 1973; Unützer et al., 2001). The SCL-20 is a widely used outcome measure in primary care trials (Katon et al., 1999; Katon et al., 1995; Kroenke et al., 2001; Williams Jr et al., 2000). The measure has demonstrated good internal consistency in previous studies (Cronbach's α = 0.84-0.86) (Lee, Schulberg, Raue, & Kroenke, 2007; Williams, Stellato, Cornell, & Barrett, 2004), as well as in the IMPACT sample recruited from the Indiana sites (Cronbach's α = 0.81 at baseline and 0.91 at 12 months). In terms of validity, the SCL-20 and PHQ-9, which is an established depression measure, have been found to be moderately correlated with one another (r = 0.54). In addition, a 50% reduction in SCL-20 score has been shown to accurately identify 79% of patients who no longer met criteria for MDD after 12 weeks of collaborative care, suggesting that this cut point is a good indicator of change in depression status (O'Connor et al., 2010). Participants who endorsed use of

antidepressants in the 3 months preceding the baseline interview received a code of '1' (yes) on this variable; otherwise, participants received a code of '0' (no).

After the baseline interview, follow-up assessments occurred at 3-, 6-, and 12-months of the intervention period. These interviews were conducted over the telephone by trained lay interviewers (Unützer, Katon, et al., 2002) who were blind to treatment assignment. Response rates for the telephone interviews were 90%, 87%, and 83% for the 3-, 6-, and 12-month calls, respectively (Unützer, Katon, et al., 2002). Depression outcome and care variables assessed during the 12-month telephone call were depressive symptom severity, as well as antidepressant use and psychotherapy received during the intervention period (Unützer, Katon, et al., 2002). To assess depression symptom severity, interviewers readministered the SCL-20. Participants who endorsed taking any antidepressants during the 12-month intervention period were coded as '1' (yes), and the percentage in each treatment group who received antidepressants during the trial was calculated. Participants who endorsed having any psychotherapy sessions during the intervention period were coded as '1' (yes), and the percentage in each treatment group who received psychotherapy during the trial was calculated. Change in depressive symptom severity over the intervention period was calculated as 12-month SCL-20 score minus baseline SCL-20 score.

2.4 Data Analysis

2.4.1 Data Cleaning and Reduction

All variables were examined for missing values. Missing data (n = 4 per treatment group) were identified only for the 12-month SCL-20 score. Because no missing data

were imputed, analyses that included the 12-month SCL-20 score or SCL-20 change variables had a total sample size of 152 participants.

Next, frequencies for categorical variables (sex, race/ethnicity, hypertension, smoking status, antidepressant use during the 3 months preceding baseline, and antidepressant use and psychotherapy during the trial) and means, standard deviations, and distributions of continuous variables (age, BMI, and pre-treatment, post-treatment, and change in SCL-20 score) were examined to ensure that these descriptive statistics were in the expected ranges. All values were found to be within range. For continuous variables, skewness and kurtosis values were also examined to evaluate the assumption of normality. Because all variables were normally distributed (skewness < 3.0 and kurtosis < 10.0; Kline, 2010), no transformations were performed.

2.4.2 Preliminary Analyses

Prior to conducting any hypothesis-testing analyses, chi-square tests (for categorical variables) and independent samples *t* tests (for continuous variables) were conducted to compare baseline characteristics between patients in the IMPACT and usual care groups. Given that randomization was not stratified by baseline diabetes status, it was especially important to evaluate whether there was covariate imbalance between the groups at baseline, as such imbalance could have suggested an alternative explanation for an apparent treatment effect. For instance, a treatment group difference in diabetes incidence could be due to an imbalance in one or more baseline variables predictive of future diabetes (e.g., BMI). Additionally, a Cohen's *d* effect size was calculated to quantify the effect of the IMPACT intervention on change in SCL-20 score.

2.4.3 Test of Hypothesis #1

Hypothesis #1: Depressed patients randomized to collaborative depression care have a lower incidence of type 2 diabetes than depressed patients randomized to usual care.

To test this hypothesis, Cox proportional hazard regression models were constructed. Cox models are a type of survival analysis that take into account the differing times to an event of interest and compare the cumulative probability of events occurring in two or more cohorts (Singh & Mukhopadhyay, 2011). Cox models yield hazard ratios (*HR*) as the primary statistic. For this study, *HR*s estimated the relative likelihood of incident diabetes in the IMPACT group versus control group. Patients were censored at their date of death or at the end of the follow-up period (December 31, 2009). Tests of the proportional hazards assumption were made using Schoenfeld residuals. Specifically, correlations between partial residuals of each covariate and rank ordered survival time were evaluated. All correlations were nonsignificant indicating that the proportional hazards assumption was met for each variable. These analyses were supplemented by examining Kaplan-Meier method plots. Specifically, plots of the log-log survival curves of time by each covariate were assessed for linearity. All relationships were linear, again indicating that the assumption was met for each variable.

For *hypothesis #1*, Cox models were constructed to test whether there were treatment group differences in the cumulative likelihood of incident diabetes over the 9-year period. The first Cox model included the randomization status variable (IMPACT vs. usual care) as the only independent variable (no covariates). Kaplan-Meier survival curves were constructed to illustrate the time from enrollment to incident diabetes for

each treatment group. The second Cox model included baseline age, sex, and race/ethnicity variables in addition to the randomization status variable (demographics-adjusted analyses), while the third Cox model further included baseline hypertension, smoking, and BMI as diabetes risk factors (Grundy et al., 2005; Mozaffarian et al., 2009) (diabetes risk factors-adjusted analyses). Then, subsequent models were constructed in which baseline variables that were significantly or meaningfully imbalanced between the treatment groups were added one at a time to the first Cox model that included the randomization status variable. The last set of Cox models were those that added the depression treatment variables (SCL-20 change, trial antidepressants, and trial psychotherapy) one at a time to the first Cox model.

2.4.3.1 Sensitivity Analyses

To examine the influence of the primary incident diabetes definition on the pattern of results, the demographics-adjusted and diabetes risk factors-adjusted analyses described in the preceding section were rerun after modifying the outcome definition. The alternative definitions were (a) secondary definition – the presence of any one of the following: ICD-9 code of 250, fasting glucose value ≥ 126 mg/dL, HbA_{1c} value ≥ 8.5%, or diabetes medication (insulin or oral hypoglycemic medication); (b) ICD-9 code of 250 alone; (c) fasting glucose value ≥ 126 mg/dL alone; (d) HbA_{1c} value ≥ 8.5% alone; and (e) diabetes medication (insulin or oral hypoglycemic medication) alone. Of note, to code the date associated with a diabetes event identified by definition (a), the earliest date among the four components (ICD-9 code, fasting glucose, HbA_{1c}, or diabetes medication)

during the follow-up period was chosen. For all alternative outcome definitions, participants who did not have an event were censored at their date of death or at the end of the follow-up period (December 31, 2009).

To examine the influence of the primary definition of baseline diabetes on the pattern of results, a secondary definition of baseline diabetes was created, defined as the presence of any one of the following: ICD-9 code of 250, fasting glucose value ≥ 126 mg/dL, HbA_{1c} value ≥ 8.5%, or diabetes medication (insulin or oral hypoglycemic medication). Using this broad definition of baseline diabetes, the unadjusted, demographics-adjusted, and diabetes risk factors-adjusted analyses were rerun with both the primary and alternative outcome definitions.

Finally, to examine the influence of our chosen cutpoint for HbA_{1c}, the primary definition for baseline diabetes, and all outcome definitions for diabetes were modified to reflect a cutpoint for HbA_{1c} of ≥ 8.0%, which represents the more conservative end of the range (between 8-9%) for diabetes diagnosis recommended for older adults in recently published guidelines (American Geriatrics Society Expert Panel on the Care of Older Adults with Diabetes Mellitus, 2013). All analyses were then rerun using these modified baseline and outcome definitions.

2.4.4 Test of Hypotheses #2-4

Hypothesis #2: Change in depressive symptoms during the trial mediates the hypothesized beneficial effect of collaborative depression care on incident diabetes.

Hypothesis #3: Antidepressant treatment received during the trial mediates the hypothesized beneficial effect of collaborative depression care on incident diabetes.

Hypothesis #4: Psychotherapy received during the trial mediates the hypothesized beneficial effect of collaborative depression care on incident diabetes.

To test *hypotheses #2-4*, three separate mediation models were constructed. Specifically, 12-month change in SCL-20 score, trial antidepressants (yes, no), and trial psychotherapy (yes, no) were added one at a time to Cox models that included the treatment main effect (randomization status variable). Percent reduction in treatment effect size after adding each potential mediator was computed as $(B_{T+M} - B_T) / B_T \times 100$, where B_{T+M} is the unstandardized coefficient for the treatment main effect in the model with the potential mediator, and B_T is the unstandardized coefficient for the same variable in the model without the mediator. These descriptive results help characterize the degree to which the treatment effect is explained by each potential mediator. Statistical mediation analyses were then performed using the SPSS macro known as 'PROCESS' (Hayes, 2012; Preacher & Hayes, 2008). Confidence intervals were obtained using nonparametric bootstrapping methods. In bootstrapping, random samples are generated based on the original data (in the current analyses, 5,000 random samples were generated). For each random sample, the mediated effects are computed. The distribution of these effects is used to obtain 95% confidence intervals for the magnitude of indirect effect. The significance of the indirect effect can be determined by assessing whether the confidence interval contains the value '0'. All analyses were performed using SPSS statistical software, version 21 (IBM Corp., Armonk, NY).

CHAPTER 3 RESULTS

3.1 Characteristics of Participants

The 75 participants with diabetes at baseline were excluded from the sample comprised of the 235 participants randomized from the Indiana sites in the IMPACT trial, resulting in a final sample of 160 participants that were equally distributed between IMPACT and usual care groups (see Figure 2 for flowchart of participants). The mean age of the total sample was 67 years (*SD* = 6.9). Twenty-three percent were male, and almost half (44%) were African-American. There was a high prevalence of diabetes risk factors at baseline, as 72% had hypertension, 36% were smokers, and 42% were obese (BMI $\geq$ 30). At baseline, 12% patients met criteria for MDD only, 35% for dysthymic disorder only, and 53% for both MDD and dysthymic disorder. The mean baseline SCL-20 score was 1.37 (*SD* = 0.53), indicating moderate depressive symptom severity. In the 3-months preceding the baseline interview, 51.9% of the sample reported taking antidepressants. Table 3 presents these baseline characteristics stratified by treatment group. Although independent sample *t* tests and chi-square tests revealed no significant group differences in these characteristics, mean BMI was numerically higher (p = .137) and mean SCL-20 score was numerically lower (p = .074) in the IMPACT group versus the usual care group.

3.2 Effect of the IMPACT Intervention on Depression Outcomes and Care

As can be seen in Table 3 and Figure 3, IMPACT patients without baseline diabetes exhibited significantly greater reductions in SCL-20 score than usual care patients (p = .013) at post-treatment, with a treatment effect size (d = 0.41) in the moderate range (Cohen, 1992). Moreover, 29% (23/80) of the IMPACT patients, versus 15% (12/80) of the usual care patients, achieved at least a 50% reduction in SCL-20 score (p = .035), which was the primary outcome by which treatment response was assessed in the entire IMPACT trial. As is also shown in Table 3, IMPACT patients were more likely to have received any psychotherapy during the trial than usual care patients (p <.001), although they were not significantly more likely to have had antidepressant use during the trial (p = .230).

3.3 Test of Hypothesis #1

Assessing incident diabetes with the primary definition (the presence of an ICD-9 diabetes code and either a positive laboratory value or diabetes medication use), 33 cases (21%) were identified during the 9-year follow-up period, of which 49% (n=16) were a combination of an ICD-9 code and a positive fasting glucose value, 30% (n=10) were a combination of an ICD-9 code and positive HbA_{1c} value, and 21% (n=7) were a combination of an ICD-9 code and diabetes medication use. Table 4 shows the event composition of the primary definition of incident diabetes in each treatment group. As can be seen, the IMPACT group was more likely than the usual care group to have received a diabetes diagnosis through a combination of an ICD-9 code and a positive laboratory value.

Contrary to Hypothesis #1, the rate of incident diabetes in the IMPACT group (22/80 = 27.5%) was twice the rate observed in the usual care group (11/80 = 13.7%). Figure 4 displays the Kaplan-Meier survival curves illustrating the time to incident diabetes for each treatment group. As can be seen, the survival curves separated early in the follow-up period, and the advantage of the usual care group continued to increase in magnitude from year 2 to year 9 of follow-up. However, a log-rank test indicated that this apparent group difference fell short of significance ($\chi^2 = 3.27$, $p = .071$).

As shown in Table 5 (primary definition), a Cox model with the randomization status variable as the only independent variable also indicated that IMPACT patients had a numerically (94%), though nonsignificant ($p = .076$), increased risk of incident diabetes compared to usual care patients. In subsequent models, IMPACT patients remained at a nonsignificant increased risk of incident diabetes after adjusting for demographic factors (94% increased risk, $p = .075$) and further adjusting for diabetes risk factors (73% increased risk, $p = .157$). In the model with all covariates, only BMI significantly predicted incident diabetes (*HR* = 1.08, 95% *CI*: 1.04-1.12, $p < .001$). Specifically, a 1-unit increase in BMI was associated with an 8% increase in the likelihood of incident diabetes.

Because baseline SCL-20 score and BMI variables were noticeably imbalanced between the treatment groups, they were added one at a time to models that included the randomization status variable. When baseline SCL-20 score was added, IMPACT patients remained at a numerically, though nonsignificant, increased risk of incident diabetes (*HR* = 2.06, 95% *CI*: 0.98-4.31, $p = .056$) compared to usual care patients. In this model, baseline SCL-20 score (*HR* = 1.35, 95% *CI*: 0.72-2.54, $p = .345$) did not predict

incident diabetes. When BMI was added, the effect size for randomization status was attenuated (*HR* = 1.64, 95% *CI*: 0.78-3.43, *p* = .192), and BMI significantly predicted incident diabetes (*HR* = 1.06, 95% *CI*: 1.03-1.10, *p* < .001). This BMI-adjusted analysis suggests that the numerically higher mean BMI of the IMPACT group than the usual care group at baseline may have, in part, contributed to the elevated rate of incident diabetes in the IMPACT group.

Then, depression treatment variables (SCL-20 change, trial antidepressants, and trial psychotherapy) were added one at a time to models that included the randomization status variable. In each of these three models, neither randomization status nor any of the depression treatment variables was significantly associated with incident diabetes (SCL-20 change model – randomization status: *HR* = 1.79, 95% *CI*: 0.84-3.78, *p* = .129; SCL-20 change: *HR* = 0.92, 95% *CI*: 0.54-1.58, *p* = .771; trial antidepressants model – randomization status: *HR* = 1.84, 95% *CI*: 0.88-3.81, *p* = .104; trial antidepressants: *HR* = 2.15, 95% *CI*: 0.82-5.60, *p* = .117; trial psychotherapy model – randomization status: *HR* = 1.66, 95% *CI*: 0.75-3.68, *p* = .211; trial psychotherapy: *HR* = 1.44, 95% *CI*: 0.68-3.04, *p* = .339). Collectively, these findings do not support *Hypothesis #1*.

3.3.1 Sensitivity Analyses

Table 5 presents the number of incident diabetes cases identified using each of the five alternative outcome definitions. There was variability in the rate of incident diabetes across these definitions, ranging from 13 events (IMPACT = 9; usual care = 4) for the HbA_{1c} only definition to 67 events (IMPACT = 37; usual care = 30) for the secondary definition (ICD-9 code OR fasting glucose OR HbA_{1c} OR diabetes medication). Across

the outcome definitions, there was also variability in the treatment group differences in incident diabetes rates, with the lowest treatment group difference observed for diabetes medication only definition (IMPACT = 13.7%; usual care = 10.0%), and the highest for the fasting glucose only definition (IMPACT = 38.7%; usual care = 25.0%).

In Cox models that included randomization status as the only independent variable, IMPACT patients had a nonsignificantly elevated risk (23% to more than two times the increased risk) of incident diabetes (see Table 5). The lowest and highest *HR*s were observed for the secondary definition (*HR* = 1.23, 95% *CI*: 0.76-1.99, *p* = .399) and for the HbA_{1c} only outcome (*HR* = 2.15, 95% *CI*: 0.66-7.00, *p* = .202), respectively. In subsequent models, IMPACT patients remained at a nonsignificant increased risk of incident diabetes after adjusting for demographic factors (20% to more than two times the increased risk) and further adjusting for diabetes risk factors (9% to 65% increased risk; see Table 5). In Cox models that adjusted for demographic factors, the lowest and highest *HR*s were again observed for the secondary definition (*HR* = 1.20, 95% *CI*: 0.74-1.96, *p* = .454) and the HbA_{1c} only outcome *(HR* = 2.12, 95% *CI*: 0.65-6.98, *p* = .215), respectively. Lastly, in Cox models further adjusting for diabetes risk factors, the lowest and highest *HR*s were observed for ICD-9 code only outcome (*HR* = 1.09,95% *CI*: 0.59-2.00, *p* = .781) and the HbA_{1c} only outcome (*HR* = 1.65, 95% *CI*: 0.47-5.75, *p* = .429), respectively. These sensitivity analyses suggest that the relationship between depression treatment and incident diabetes events does not vary by the type of diabetes outcome definition used, although the nonsignificant elevation in risk for the IMPACT group does vary numerically across the definitions. Although the treatment group difference is consistently larger for the HbA_{1c} only outcome, the low event rate and large confidence

intervals for this outcome render interpretation difficult. It should be noted that across the diabetes definitions assessed, adjusting for BMI reduced the treatment group difference, again implicating the baseline BMI imbalance as a partial explanation for the elevated incidence rate in the IMPACT group. Taken together, these sensitivity analyses do not support *Hypothesis #1*.

Using the broad definition of baseline diabetes [any one of the following: ICD-9 code of 250, fasting glucose value ≥ 126 mg/dL, HbA_{1c} value ≥ 8.5%, or diabetes medication (insulin or oral hypoglycemic medication)] resulted in a cohort of 120 participants (IMPACT: *n*=60; Usual Care: *n*=60). Table 6 presents the number of incident diabetes cases identified in this smaller cohort using each of the five alternative outcome definitions. There was again variability in the rate of incident diabetes across these definitions, ranging from 6 events (IMPACT = 6; usual care = 0) for the HbA_{1c} only definition to 40 events (IMPACT = 23; usual care = 17) for the secondary definition (ICD-9 code OR fasting glucose OR HbA_{1c} OR diabetes medication). There was also variability in the treatment group differences in incident diabetes rates, with the lowest and highest treatment group differences observed for the HbA_{1c} only definition (IMPACT = 5.0%; usual care = 0.0%) and the primary definition (IMPACT = 20.0%; Usual Care = 6.7 %) respectively. Overall, IMPACT patients remained at nonsignificant increased risk of incident diabetes in unadjusted (35% for the secondary definition to nearly three times the increased for the primary definition), demographic factors-adjusted (38% for the secondary definition to nearly five times the increased risk for the diabetes medication only definition), and diabetes risk factor-adjusted (17% for the fasting glucose only definition to more than 5 times the increased risk for the diabetes medication only

definition) analyses. Across all analyses, these low event rates and large confidence intervals continue to render interpretation difficult, but suggest that the relationship between depression treatment and incident diabetes events does not vary by the type of diabetes baseline definition used. These sensitivity analyses do not support *Hypothesis #1*.

Finally, using a more conservative HbA_{1c} cutpoint of ≥8% resulted in a cohort of 159 participants (IMPACT: *n*=79; Usual Care: *n*=80). As can be seen in Table 7, the number of total incident diabetes events (33), those for each of the five alternative outcome definitions, as well as the pattern of results for unadjusted, demographic factors-adjusted, and diabetes risk factor-adjusted all remained similar to those reported in Table 5. The one exception was the slightly greater number of incident diabetes events for the HbA_{1c} only outcome (16; IMPACT: n=10; Usual Care; n=6) due to the use of the lower end of the HbA_{1c} range (8%). This slightly greater number of events however did not change the pattern of results for the HbA_{1c} only outcome analyses.

3.4 Test of Hypothesis #2-4

Hypotheses #2-4 posited that change in depressive symptoms (*Hypothesis #2),* antidepressant treatment received (*Hypothesis #3),* and psychotherapy received (*Hypothesis #4*) during the trial would mediate the hypothesized beneficial effect of collaborative depression care on incident diabetes. These analyses, which were dependent on the outcome of *Hypotheses #1,* were not conducted for the following critical reason: the analyses for *Hypothesis #1* indicated no beneficial effect of collaborative depression care on incident diabetes. In other words, *Hypotheses #1* was not supported. It should be

noted that, under normal circumstances, a significant path ‘c’ (depression treatment to incident diabetes) association is not required to test for mediation effects (Hayes, 2012). However, in this instance, IMPACT patients had a nonsignificantly *elevated* risk of incident diabetes compared to usual care patients. Because the treatment effect was found to be trending in the opposite direction of that hypothesized in *Hypothesis # 1*, there is no theoretical rationale to pursue *Hypotheses #2-4.* Had the treatment effect been in the expected direction but falling short of statistical significance, mediation analyses testing *Hypotheses #2-4* would have been conducted as proposed.

CHAPTER 4 DISCUSSION

4.1 Summary of Study Findings

The primary objective of this follow-up study was to examine the effect of a 12-month collaborative care program for late-life depression on the 9-year risk of incident diabetes among depressed older adults initially free of diabetes. To achieve this objective, a unique combination of resources was examined – namely, IMPACT trial data linked with electronic medical record data and Medicare/Medicaid data. The IMPACT trial found that 45% of the intervention patients, versus 19% of the usual care patients, achieved a 50% reduction in depressive symptom severity at 12-month follow-up (Unützer, Katon, et al., 2002). These positive results, combined with the other available data sources, made possible the evaluation of the long-term effect of successful depression treatment on incident diabetes. This study had the potential to identify depression as a modifiable risk factor for diabetes and, consequently, depression treatment as a new target of diabetes prevention efforts.

Before testing the study hypotheses, it was important to exclude participants with diabetes at baseline. Thus, seventy-five of the 235 (32%) participants from the Indiana sites of the IMPACT trial were excluded. This prevalence of baseline diabetes is comparable to that found among older adults in the U.S. (Go et al., 2013). Importantly, excluding these participants (n = 40 from the IMPACT arm, n = 35 from the usual care

group) did not appear to imbalance the treatment groups with respect to sample size or baseline characteristics. After these exclusions, 80 participants remained each treatment group. Additionally, although baseline BMI was numerically higher and baseline SCL-20 score was numerically lower in the IMPACT group, there were no significant differences in baseline characteristics between the treatment groups. Nonetheless, it should be kept in mind that randomization in the IMPACT trial was not stratified by baseline diabetes status, leaving open the possibility that the treatment groups had imbalance on key factors, which may not have been measured.

Similar to the entire IMPACT trial (Unützer, Katon, et al., 2002) and other depression trials of older adults (Katon et al., 2004), IMPACT patients without baseline diabetes exhibited significantly greater reductions in depressive symptoms than usual care patients and were also more likely to have had any psychotherapy during the trial. However, there was no significant difference between groups in antidepressant use during the trial. It is worth mentioning that the questions assessing the type of treatment received during the intervention period were yes-no questions. This type of assessment does not provide any information about the quality and quantity of treatment received, such as the number of psychotherapy sessions completed, and the dose and duration of antidepressants received during the trial. The assessment of antidepressant use is a particularly important issue because it may have masked key differences between groups. Even though the rate of antidepressant medication use was similarly high in both treatment groups, patients in the usual care group may have received an inadequate dose and duration, which is often the case in primary care settings (Simon, 2002). In contrast, patients in the IMPACT group may have received the dose and duration of antidepressant

treatment consistent with clinical recommendations. Together, the higher likelihood of receiving psychotherapy and perhaps of receiving the recommended antidepressant treatment may be responsible for the greater reductions in depressive symptoms observed in the IMPACT group versus the usual care group.

Despite improvement in depressive symptoms, the primary hypothesis (*Hypothesis #1*) that depressed patients randomized to collaborative depression care, versus usual care, would have a lower incidence of type 2 diabetes was not supported. Cox model results showed no significant treatment group differences in incident diabetes before and after adjustment for demographic and diabetes risk factors, and in sensitivity analyses in which alternative definitions of incident diabetes were modeled. Collectively, these analyses suggest that depression treatment alone did not have much influence on long-term diabetes incidence. In fact, the rate of incident diabetes in the IMPACT group was twice that in the usual care group, with Cox models confirming that the IMPACT group had a nonsignificantly elevated risk (94%). In all models, adjusting for BMI attenuated the nonsignificantly elevated treatment group difference and BMI was a significant predictor of incident diabetes, suggesting that the baseline BMI imbalance may have contributed to the elevated rate of incident diabetes in the IMPACT group. Across alternative outcome definitions modeled in sensitivity analyses, the degree of nonsignificant elevation of the IMPACT group varied numerically, with the greatest treatment group difference observed for the HbA_{1c} only outcome. Finally, Cox models adjusting for depression treatment variables did not change the pattern of results and none of these depression variables were associated with incident diabetes. Given the absence of any support for *Hypothesis #1*, I did not pursue analyses evaluating change in

depressive symptoms and antidepressants and psychotherapy received during the trial as potential mediators of the beneficial effect of collaborative depression care on incident diabetes (*Hypotheses #2-4)*. To summarize, the findings of this long-term follow-up of the IMPACT trial suggest that depression treatment alone is not sufficient to lower the diabetes risk of older depressed patients.

4.2 Fit with Existing Literature

The present results are both inconsistent and consistent with the existing literature. These findings are inconsistent with considerable epidemiologic evidence suggesting that depression is an independent risk factor for diabetes (see 'Epidemiologic studies' section in the Introduction), and they do not align with results of some past clinical studies involving non-diabetic samples. In two separate studies conducted by Weber-Hamann et al. (2006, 2008), patients with depression but not diabetes who were given either tricyclic or SSRI antidepressants and who achieved remission showed improved insulin sensitivity over a 5- to 8-week period. It should be noted, however, that in the larger of these two studies, depression remission was positively associated with only one of three diabetes outcomes examined (insulin concentration 120 minutes after a glucose ingestion challenge but not fasting insulin and glucose levels). In another study, Okamura et al. (2000) reported that non-diabetic patients with depression who received either tricyclic or tetracyclic antidepressants showed significant improvement in insulin sensitivity from pre- to post-treatment, as assessed by oral glucose tolerance tests. Yet, because all three studies did not include a control group, it is unclear if the same pattern of results would have been found if patients receiving antidepressant therapy were

compared to those receiving placebo or usual care. The present results are consistent with those of Kauffman et al. (2005), who showed that 8 weeks of an SSRI treatment did not produce improvement in insulin sensitivity, as measured by oral glucose tolerance tests. Yet, these results are not easily comparable to those of the present study because of their dissimilar sample of 32 depressed and nondepressed women of reproductive age who were euglycemic at baseline. This discussion highlights the dearth of past studies involving samples of depressed patients initially free of diabetes and illustrates the lack of methodological rigor of these studies (e.g., small sample size, lack of randomization, and absence of a control group). Despite the null findings, the present study contributes to this limited literature by: (a) utilizing data from a well-designed clinical trial in which participants were randomized to intervention arms, (b) excluding participants with diabetes at baseline, and (c) including a long follow-up period to identify cases of incident diabetes.

Interestingly, the present results also parallel those of some studies involving patients with comorbid depression and diabetes. In this literature, only 1 in 4 previous trials have found a significant association between effective depression treatment and indices of glycemic control (see 'Treatment studies' section in the Introduction). Moreover, of the studies that did find improvement in glycemic control, several also included diabetes self-management training in addition to cognitive-behavioral therapy or supportive therapy for depression (Van der Feltz-Cornelis et al., 2010). Due to the combination of interventions, it is unclear whether depression treatment, diabetes self-management training, or both were responsible for the improvement in glycemic control. Of note, among the studies that reported null findings is a study that also utilized data

from the IMPACT trial (Williams et al., 2004). In a preplanned subgroup analysis of 417 participants with both depression and diabetes, it was found that, although HbA_{1c} levels decreased slightly (7.28% to 7.11%), the IMPACT intervention did not significantly improve glycemic control.

Although investigators have proposed several explanations for these null findings, they do not appear to be applicable to the present study. For instance, one proposed explanation is that the post-treatment assessment of glycemic control may have been premature if improvement in glycemic control lags behind improvement in depressive symptoms. This explanation is not applicable here, given the 9-year follow-up period. Another potential explanation is that there was limited margin to detect improvement in glycemic control due to good glycemic control at baseline. Again, this explanation does not seem applicable here, as IMPACT participants had an elevated risk of type 2 diabetes due to their older age and high diabetes risk factor burden. Nonetheless, there are other plausible explanations for the null results of the present study, which are discussed in the next section.

4. 3 Possible Explanations for Numerically Elevated Diabetes Risk in the Treatment Arm

There are at least three possible explanations for the numerically, although nonsignificantly, elevated diabetes risk in the IMPACT group. One possible explanation is the numerically higher BMI at baseline in the IMPACT group (31.1) versus the usual care group (29.1). Due to this higher BMI, the degree of insulin resistance and the prevalence of pre-diabetes may have been greater in the IMPACT group. Thus, it is reasonable that a higher percentage of patients in this arm would transition to diagnosed,

clinical diabetes during follow-up. The BMI-adjusted analyses provide some support for this notion, as adjusting for baseline BMI attenuated the numerically elevated diabetes risk of the IMPACT group across models (see Table 5). Also of relevance, baseline BMI predicted incident diabetes. However, this adjustment did not eliminate the numerically elevated diabetes risk of the IMPACT group, suggesting that other factors are also involved.

Another possible explanation is the potential detrimental side effects of antidepressant medication on insulin resistance and type 2 diabetes. Specifically, one direct physiologic effect of SSRIs – the primary type of antidepressant medication received by participants – is appetite promotion and weight gain (Ferguson, 2001). In turn, weight gain exacerbates insulin resistance and, subsequently, can lead to the development of type 2 diabetes (Ismail, 2010). Thus, if the IMPACT group did receive a higher dose and longer duration of SSRI treatment, it may have promoted the development of diabetes. Results from the present study, although providing some support for this explanation, also suggest that antidepressant use alone does not explain the higher diabetes incidence in the IMPACT group. On the one hand, antidepressant use during the trial was associated with a numerically, though nonsignificantly, higher risk of incident diabetes (*HR* = 2.15). On the other hand, adjusting for antidepressant use during the trial only slightly attenuated the treatment effect on incident diabetes (from *HR* = 1.94 to *HR* = 1.84).

A related possibility is that successful depression treatment in the IMPACT arm may have had detrimental effects on obesity as a primary hypothesized mechanism underlying the depression-to-diabetes relationship. Specifically, it is possible that

alleviation of depression may have resulted in increased appetite and caloric intake in a fashion similar to the weight promoting consequences of smoking cessation. This weight gain in the IMPACT arm may have led to obesity and diabetes development at a greater rate over the follow-up period.

A third possible explanation is that the increased incidence of diabetes in the IMPACT group is due to greater detection of diabetes in this group. First, IMPACT patients had greater contact with health care providers (DCSs contacted patients at least every other week) and were probably more likely to have been referred for other health/social services when indicated (which was one of the DCS's tasks). Greater contact with the health care system could have led the IMPACT group to have an increased chance of being assessed for new-onset medical conditions, including diabetes. Consistent with this notion, 19 of the 22 (86%) diabetes cases in the IMPACT group, versus only 7 of the 11 (64%) diabetes cases in the usual care group were due to the presence of a diabetes ICD-9 code and a positive laboratory value, suggesting that laboratory tests may have been conducted more often in the IMPACT group. Second, IMPACT patients exhibited greater improvements in depression during the trial and may have had a lower rate of depression relapse during follow-up due to receiving problem-solving therapy, a type of cognitive-behavioral therapy (Gloaguen, Cottraux, Cucherat, & Blackburn, 1998). Lower levels of depression severity and rates of depression relapse may have lead IMPACT patients to be more engaged in their medical care (e.g., missing few health care visits; Bowser, Utz, Glick, & Harmon, 2010; DiMatteo, Lepper, & Croghan, 2000), which could also have led to a greater detection of new-onset diabetes.

4.4 Possible Explanations for Null Effect of Collaborative Depression Care on Diabetes Risk

Three possible explanations for the null effect of collaborative depression care on diabetes risk are: (a) the lack of a sufficient effect on the mechanisms leading to the development of diabetes, (b) the older age of the IMPACT sample, and (c) ascertainment bias.

Regarding the first possible explanation, it is conceivable that successful depression treatment alone may not have salutary effects on the hypothesized mechanisms underlying the prospective relationship between depression and diabetes (see Figure 1). Supporting this notion, Lin et al. (2006) found that depression treatment improved adherence and diabetes control in the IMPACT sample, but in a sample with existing diabetes. Moreover, other studies have found that enhanced depression care does not result in increased adherence to health behavior recommendations in cardiac patients (Huffman et al., 2011). For example, Kronish et al. (2012) reported that acute coronary syndrome patients who received depression treatment (psychotherapy and/or antidepressant medication) did not exhibit improved adherence to cardiovascular risk-reducing behaviors, including taking aspirin daily, exercising regularly, and following a healthy diet. Similarly, other studies suggest that successful depression treatment does not dampen HPA axis hyperactivation (Appelhof et al., 2006; Kauffman et al., 2005). Finally, although the IMPACT group demonstrated a reduction in depressive symptoms, it is possible that the magnitude of this reduction was not sufficient to lead to improvement in the hypothesized mechanisms. Results of a number of past studies

suggest that remission of depression is necessary to improve diabetes markers (Kauffman et al., 2005; Okamura et al., 2000; Weber-Hamann et al., 2006; Weber-Hamann et al., 2008).

A second possible explanation for the null effect of collaborative depression care on diabetes risk is the older age of the sample. Because insulin resistance increases with age (Centers for Disease Control and Prevention, 2011), its severity in the IMPACT sample, despite the absence of diagnosed diabetes, was likely high. In addition, there was a high prevalence of diabetes risk factors (e.g., BMI) in the sample at baseline (see Table 3). Together, the older age and, therefore, severity of insulin resistance of this cohort, in conjunction with its high baseline diabetes risk factors status, may have overridden any effect of depression treatment on diabetes incidence.

A third possible explanation for the null results is ascertainment bias – i.e., the possibility of systematic distortion in the measurement of the true frequency of a phenomenon (in this case, diabetes incidence). Ascertainment bias is a concern because only RMRS and CMS data were used to identify new cases of diabetes. Thus, only those patients who had their diabetes detected and diagnosed were considered to be diabetes cases; patients with undiagnosed diabetes were not detected. As was discussed in the preceding section, IMPACT patients had greater contact with the health care system during the trial and may have greater contact during the follow-up period. Therefore, there were more opportunities for the IMPACT patients to have their diabetes detected and diagnosed. This lack of systematic assessment of the presence of new-onset diabetes for all randomized patients may have resulted in an underestimation of the true incidence of diabetes, especially in the usual care group.

4.5 Secondary Analysis of the Beating the Blues for Your Heart Pilot Trial

To explore whether depression treatment may have a beneficial effect on markers of diabetes risk when a systematic assessment of the outcome is performed, existing data from a separate small randomized controlled trial was examined. In the Beating the Blues for Your Heart pilot trial (PI: Stewart; ClinicalTrials.gov link: NCT01605552), depressed patients with no known CVD were recruited from local primary care clinics. Participants were randomized to an 8-session, empirically supported, computerized cognitive-behavioral intervention for depression known as Beating the Blues® or to usual care. After three months, Beating the Blues patients exhibited greater pre- to post-treatment decreases in SCL-20 scores than usual care patients (d = 1.33, p = .02). In a secondary analysis of the randomized participants without self-reported diabetes at baseline (Beating the Blues: n = 6, usual care: n = 12), fasting glucose values were examined as the outcome. Over the 3-month intervention period, Beating the Blues patients demonstrated decreases in fasting glucose levels (mean change = -3.52 mg/dL), whereas usual care patients exhibited increases (mean change = +3.15 mg/dL). Although change in fasting glucose levels from pre- to post-treatment did not reach statistical significance (post-treatment adjusted for pre-treatment level: p = .101), the effect size was in the moderate-to large range (d = 0.88).

Several differences in study design between this pilot trial and the IMPACT trial should be noted. These differences are: (a) sample age: patients aged 40+ years versus 60+ years, (b) type of intervention: computerized cognitive-behavioral intervention versus collaborative care intervention, (c) duration of intervention: 3 months versus 12 months, (d) duration of follow-up: 3 months versus 9 years, and (e) outcome: change in

glucose levels (systematically assessed) versus incident diabetes (not systematically assessed). The younger age of the Beating the Blues patients is a key advantage because 40-60 years is when type 2 diabetes onset typically occurs (Go et al, 2013). Additionally, the use of an outcome that was systematically assessed at the end of the intervention period is a key advantage, as it greatly minimizes the potential for ascertainment bias. Results of this secondary analysis (a) suggest that it would be premature to draw firm conclusions from the present analysis of the IMPACT data and (b) raise the possibility that treating depression among depressed, middle-aged adults without diabetes holds promise for lowering diabetes risk.

4.6 Limitations

As with all studies, the present study has limitations, including ascertainment bias, its post hoc nature, the lack of data for other diabetes risk factors, the primary definition of incident diabetes, and external validity. Ascertainment bias is discussed in the preceding section. The present study is post hoc in nature because the multisite IMPACT trial was not originally designed to test the study hypotheses, and consequently, randomization was not stratified by baseline diabetes status. While patients without diabetes were equally distributed across the treatment groups, no significant group differences in baseline characteristics were observed, and a strong theoretical rationale was present, only a prospective randomized controlled trial specifically designed to test the study hypotheses would allow for definitive conclusions to be drawn. Because the IMPACT study was not designed to assess diabetes outcomes, some diabetes risk factors were not assessed at baseline, such as physical inactivity and excessive alcohol use. Thus,

it is unknown if the treatment groups differed in these characteristics at baseline. The primary definition of incident diabetes was by no means definitive, and other potential definitions could have been used. This definition was chosen because it was likely to provide the best balance of sensitivity and specificity, although this could not be evaluated empirically. Of note, the prevalence rate of diabetes obtained using the primary definition is similar those found in other samples of older adults (Go et al., 2013). The external validity of the current findings is also a concern. Because the IMPACT participants were older and had high diabetes risk factor burden, the present findings might not generalize to healthier and middle-aged or younger adults.

4.7 Future Directions and Recommendations

Because the present results are not definitive due to the aforementioned methodological issues, further research is needed to determine whether depression treatment lowers diabetes risk. A potential next step for this area of research would be to conduct a moderately-sized, phase II trial involving depressed patients aged 40-60 years who are free of diabetes. This trial could use a continuous, intermediate diabetes endpoint, such as insulin resistance, as the primary outcome. There are several methodological features this trial should possess to enhance the validity of the findings. First, this trial should include a priori designation of hypotheses and outcomes, as well as power calculations to determine the sample size necessary to detect effects if they exist. Second, this trial should include a systematic assessment of diabetes outcomes to ensure that ascertainment bias is not an issue. Ideally, outcomes would be assessed immediately after the intervention period, as well as after a reasonable follow-up period. Third, this

trial should also collect long-term clinical data, such as new-onset diabetes. Because gains in clinical outcomes often lag behind gains in affective status (Rost, Nutting, Smith, Elliott, & Miriam Dickinson, 2002), assessing clinical outcomes immediately after the intervention period may miss group differences that emerge later. Fourth, this trial should deliver a depression intervention that results in depression remission for a high percentage of patients in the treatment arm. Several studies have reported that depression remission is necessary to improve diabetes-related outcomes (Lustman et al., 2006, 2007a, 2008). Lastly, this ideal study should also detect the possible harmful effect of depression treatment on weight and, thus, diabetes risk markers by assessing these factors in a rigorous manner. In sum, a phase II trial that includes the methodological features described above would provide a stronger test of the hypotheses of the present study.

If future well-designed and executed trials determine that depression treatment does not lower diabetes risk, then identifying other approaches for reducing the elevated diabetes risk of depressed patients need to be identified. One approach would be to treat the biological and/or behavioral mechanisms underlying the depression-diabetes association along with depression. The current cornerstones of diabetes prevention are non-pharmacological interventions that include physical activity and dietary components. In the Diabetes Prevention Program, an intensive lifestyle intervention was found to be effective in restoring normal glucose levels and reducing the incidence of diabetes in adults at high risk (Knowler et al., 2002). For depressed patient who are at risk for type 2 diabetes, an integrated biopsychosocial treatment program that includes comprehensive depression care and a lifestyle intervention may help to reduce diabetes risk. One

intriguing hypothesis that a trial of an integrated intervention could test is whether the combination of depression and lifestyle interventions is superior to the lifestyle intervention alone in lowering diabetes risk.

4.8 Conclusions

Altogether, the results of this 9-year follow-up of the IMPACT trial suggest that effective depression treatment alone may not be necessary or sufficient to reduce diabetes incidence among depressed, older adults. These findings are inconsistent with preliminary findings of smaller intervention studies, including the secondary analysis of the Beating the Blues for Your Heart trial presented above. Possible explanations for the null findings of this study include the lack of a sufficient treatment effect on the mechanisms leading to the development of diabetes, the older age of the IMPACT sample, and ascertainment bias. Due to these methodological issues and the inconsistent findings across studies, it remains an open question as to whether depression treatment alone lower diabetes risk. Future prospective randomized controlled trials are needed to definitively test the present study's hypotheses. If these trials yield positive results, it would identify depression as a causal risk factor for diabetes and encourage providers toincorporate depression treatments in diabetes prevention efforts.

LIST OF REFERENCES

LIST OF REFERENCES

Agency for Health Care Policy and Research Depression Guideline Panel. (1993). *Depression in Primary Care. Volume 1. Detection and Diagnosi; Volume 2. Treatment of Major Depression. Clinical Practice Guideline No. F. AHCPR Publication Nos. 93-0550 & 93-0551*. Rockville, MD: U.S. Dept of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research.

Ainsworth, B. E., Haskell, W. L., Leon, A. S., Jacobs, D. R., Montoye, H. J., Sallis, J. F., & Paffenbarger, R. S. (1993). Compendium of physical activities: classification of energy costs of human physical activities. *Medicine and Science in Sports and Exercise, 25*(1), 71-80.

Ali, S., Stone, M., Peters, J., Davies, M., & Khunti, K. (2006). The prevalence of co-morbid depression in adults with Type 2 diabetes: a systematic review and meta-analysis. *Diabetic Medicine, 23*(11), 1165-1173.

American Diabetes Association. (2010). Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care, 33*(Supplement 1), S62-S69. doi: 10.2337/dc12-s064

American Diabetes Association. (2013). Economic Costs of Diabetes in the U.S. in 2012. *Diabetes Care, 36*(4), 1033-1046. doi: 10.2337/dc12-2625

American Geriatrics Society Expert Panel on the Care of Older Adults with Diabetes Mellitus. (2013). Guidelines Abstracted from the American Geriatrics Society Guidelines for Improving the Care of Older Adults with Diabetes Mellitus: 2013 Update. *Journal of the American Geriatrics Society, 61*(11), 2020-2026. doi: 10.1111/jgs.12514

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders (4th ed., text rev.) DSM-IV-TR*. Washington, DC: Author.

Anderson, R. J., Freedland, K. E., Clouse, R. E., & Lustman, P. J. (2001). The prevalence of comorbid depression in adults with diabetes a meta-analysis. *Diabetes Care, 24*(6), 1069-1078.

Appelhof, B. C., Huyser, J., Verweij, M., Brouwer, J. P., van Dyck, R., Fliers, E., . . . Schene, A. H. (2006). Glucocorticoids and relapse of major depression (dexamethasone/corticotropin-releasing hormone test in relation to relapse of major depression). *Biological Psychiatry, 59*(8), 696-701.

Arroyo, C., Hu, F. B., Ryan, L. M., Kawachi, I., Colditz, G. A., Speizer, F. E., & Manson, J. (2004). Depressive symptoms and risk of type 2 diabetes in women. *Diabetes Care, 27*(1), 129-133.

Bi, Y., Wang, T., Xu, M., Xu, Y., Li, M., Lu, J., . . . Ning, G. (2012). Advanced research on risk factors of type 2 diabetes. *Diabetes/Metabolism Research and Reviews, 28*(s2), 32-39.

Boden, G., & Shulman, G. (2002). Free fatty acids in obesity and type 2 diabetes: defining their role in the development of insulin resistance and β-cell dysfunction. *European Journal of Clinical Investigation, 32*(s3), 14-23.

Bowser, D. M., Utz, S., Glick, D., & Harmon, R. (2010). A Systematic Review of the Relationship of Diabetes Mellitus, Depression, and Missed Appointments in a Low-Income Uninsured Population. *Archives of Psychiatric Nursing, 24*(5), 317-329. doi: http://dx.doi.org/10.1016/j.apnu.2009.12.004

Brown, A., Mangione, C., Saliba, D., & Sarkisian, C. (2003). California Healthcare Foundation/American Geriatrics Society Panel on Improving Care for Elders with Diabetes. Guidelines for improving the care of the older person with diabetes mellitus. *J Am Geriatr Soc, 51*(5), S265-S280.

Brown, L. C., Majumdar, S. R., Newman, S. C., & Johnson, J. A. (2005). History of depression increases risk of type 2 diabetes in younger adults. *Diabetes Care, 28*(5), 1063-1067.

Callahan, C. M., Unverzagt, F. W., Hui, S. L., Perkins, A. J., & Hendrie, H. C. (2002). Six-item screener to identify cognitive impairment among potential subjects for clinical research. *Medical Care, 40*(9), 771.

Canoy, D., Wareham, N., Luben, R., Welch, A., Bingham, S., Day, N., & Khaw, K.-T. (2005). Cigarette Smoking and Fat Distribution in 21, 828 British Men and Women: A Population-based Study. *Obesity Research, 13*(8), 1466-1475. doi: 10.1038/oby.2005.177

Carnethon, M. R., Biggs, M. L., Barzilay, J. I., Smith, N. L., Vaccarino, V., Bertoni, A. G., . . . Siscovick, D. (2007). Longitudinal association between depressive symptoms and incident type 2 diabetes mellitus in older adults: the cardiovascular health study. *Archives of Internal Medicine, 167*(8), 802.

Carnethon, M. R., Kinder, L. S., Fair, J. M., Stafford, R. S., & Fortmann, S. P. (2003). Symptoms of depression as a risk factor for incident diabetes: findings from the National Health and Nutrition Examination Epidemiologic Follow-up Study, 1971–1992. *American Journal of Epidemiology, 158*(5), 416-423.

Centers for Disease Control and Prevention. (2011). National Diabetes Fact Sheet: National Estimates and General Information on Diabetes and Prediabetes in the United States, 2011. Atlanta, Georgia: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention.

Centers for Disease Control and Prevention. (2012). *Diabetes Report Card 2012*. Atlanta, GA: Centers for Disease Control and Prevention, Us Department of Health and Human Services.

Chang, S. A. (2012). Smoking and type 2 diabetes mellitus. *Diabetes & Metabolism Journal, 36*(6), 399-403.

Cohen, J. (1992). A power primer. *Psychological Bulletin, 112*(1), 155.

Derogatis, L. R., Lipman, R. S., & Covi, L. (1973). SCL-90: an outpatient psychiatric rating scale--preliminary report. *Psychopharmacology Bulletin, 9*(1), 13-28.

DiMatteo, M. R., Lepper, H. S., & Croghan, T. W. (2000). Depression is a risk factor for noncompliance with medical treatmentMeta-analysis of the effects of anxiety and depression on patient adherence. *Archives of Internal Medicine, 160*(14), 2101-2107.

Eaton, W. W., Armenian, H., Gallo, J., Pratt, L., & Ford, D. E. (1996). Depression and risk for onset of type II diabetes: a prospective population-based study. *Diabetes Care, 19*(10), 1097-1102.

Ell, K., Katon, W., Xie, B., Lee, P.-J., Kapetanovic, S., Guterman, J., & Chou, C.-P. (2010). Collaborative Care Management of Major Depression Among Low-Income, Predominantly Hispanic Subjects With Diabetes A randomized controlled trial. *Diabetes Care*, *33*(4), 706-713.

Elliott, W. J., & Meyer, P. M. (2007). Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. *The Lancet*, *369*(9557), 201-207.

Everson-Rose, S. A., Meyer, P. M., Powell, L. H., Pandey, D., Torréns, J. I., Kravitz, H. M., . . . Matthews, K. A. (2004). Depressive symptoms, insulin resistance, and risk of diabetes in women at midlife. *Diabetes Care*, *27*(12), 2856-2862.

Fava, M., & Kendler, K. S. (2000). Major depressive disorder. *Neuron*, *28*(2), 335-341.

Ferguson, J. M. (2001). SSRI antidepressant medications: adverse effects and tolerability. *Primary care companion to the Journal of Clinical Psychiatry*, *3*(1), 22.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (2002). Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Non-patient Edition (SCID-I/NP): New York: Biometrics Research, New York State Psychiatric Institute.

Fountoulakis, K. N., Gonda, X., Rihmer, Z., Fokas, C., & Iacovides, A. (2008). Revisiting the Dexamethasone Suppression Test in unipolar major depression: an exploratory study. *Ann Gen Psychiatry*, *7*(22), 1-9.

Gloaguen, V., Cottraux, J., Cucherat, M., & Blackburn, I. M. (1998). A meta-analysis of the effects of cognitive therapy in depressed patients. *Journal of Affective Disorders*, *49*, 59-72.

Go, A. S., Mozaffarian, D., Roger, V. L., Bengamin, E. J., Berry, J. D., Borden, W. B., . . . Franco, S. (2013). Heart disease and stroke statistics--2013 update: a report from the American Heart Association. *Circulation., 127*(1), e6-e245. doi: 10.1161/CIR.0b013e31828124ad.

Golden, S. H. (2007). A review of the evidence for a neuroendocrine link between stress, depression and diabetes mellitus. *Current Diabetes Reviews, 3*(4), 252-259.

Golden, S. H., Lazo, M., Carnethon, M., Bertoni, A. G., Schreiner, P. J., Roux, A. V. D., . . . Lyketsos, C. (2008). Examining a bidirectional association between depressive symptoms and diabetes. *JAMA: the journal of the American Medical Association, 299*(23), 2751-2759.

Golden, S. H., Williams, J. E., Ford, D. E., Yeh, H.-C., Sanford, C. P., Nieto, F. J., & Brancati, F. L. (2004). Depressive symptoms and the risk of type 2 diabetes the atherosclerosis risk in communities study. *Diabetes Care, 27*(2), 429-435.

Goldston, K., & Baillie, A. J. (2008). Depression and coronary heart disease: a review of the epidemiological evidence, explanatory mechanisms and management approaches. *Clinical Psychology Review, 28*(2), 288-306.

Gress, T. W., Nieto, F. J., Shahar, E., Wofford, M. R., & Brancati, F. L. (2000). Hypertension and Antihypertensive Therapy as Risk Factors for Type 2 Diabetes Mellitus. *New England Journal of Medicine, 342*(13), 905-912. doi: doi:10.1056/NEJM200003303421301

Grøntved, A., & Hu, F. B. (2011). Television viewing and risk of type 2 diabetes, cardiovascular disease, and all-cause mortality. *JAMA: Journal of the American Medical Association, 305*(23), 2448.

Grundy, S. M., Cleeman, J. I., Daniels, S. R., Donato, K. A., Eckel, R. H., Franklin, B. A., . . . Costa, F. (2005). Diagnosis and Management of the Metabolic Syndrome: An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation, 112*(17), 2735-2752. doi: 10.1161/circulationaha.105.169404

Haffner, S. M. (2003). Insulin resistance, inflammation, and the prediabetic state. *The American Journal of Cardiology, 92*(4), 18-26.

Handelsman, Y., Mechanick, J., Blonde, L., Grunberger, G., Bloomgarden, Z., Bray, G., . . . Wyne, K. (2011). American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for Developing a Diabetes Mellitus Comprehensive Care Plan. *Endocrine Practice, 17*(0), 1-53. doi: 10.4158/EP.17.S2.1

Hayes, A. (2012). PROCESS: A versatile computational tool for observed variable mediation, moderation, and conditional process modeling. *[White paper]*.

Hegel, M., Barrett, J., Oxman, T., Mynors-Wallis, L., & Gath, D. (1999). Problem-solving treatment for primary care (PST-PC): a treatment manual for depression. *Hanover, NH: Dartmouth University*.

Hennessy, S., Leonard, C. E., Palumbo, C. M., Newcomb, C., & Bilker, W. B. (2007). Quality of Medicaid and Medicare data obtained through Centers for Medicare and Medicaid Services (CMS). *Medical Care, 45*(12), 1216-1220.

Henry, R. R. (2003). Insulin resistance: from predisposing factor to therapeutic target in type 2 diabetes. *Clinical Therapeutics, 25*, B47.

Howren, M. B., Lamkin, D. M., & Suls, J. (2009). Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosomatic Medicine, 71*(2), 171-186.

Hu, F. B., Li, T. Y., Colditz, G. A., Willett, W. C., & Manson, J. E. (2003). Television watching and other sedentary behaviors in relation to risk of obesity and type 2 diabetes mellitus in women. *JAMA: Journal of the American Medical Association, 289*(14), 1785-1791.

Hu, F. B., Manson, J. E., Stampfer, M. J., Colditz, G., Liu, S., Solomon, C. G., & Willett, W. C. (2001). Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *New England Journal of Medicine, 345*(11), 790-797.

Huffman, J. C., Mastromauro, C. A., Sowden, G., Fricchione, G. L., Healy, B. C., & Januzzi, J. L. (2011). Impact of a depression care management program for hospitalized cardiac patients. *Circulation: Cardiovascular Quality and Outcomes, 4*(2), 198-205.

International Diabetes Federation. (2009). *Diabetes Atlas* (4th ed.). Brussels: International Diabetes Federation.

Ismail, K. (2010). Unraveling the Pathogenesis of the Depression–Diabetes Link *Depression and Diabetes* (pp. 29-61).

Kahn, C. R. (2001a). Etiology and pathogenesis of type 2 diabetes mellitus and related disorders. In K. L. Becker (Ed.), *Principles and Practice of Endocrinology and Metabolism* (Third ed., pp. 1315-1319). Philadelphia, PA: Lippincott Williams and Wilkins.

Kahn, C. R. (2001b). Glucose Homeostasis and Insulin Action. In K. L. Becker (Ed.), *Principles and Practice of Endocrinology and Metabolism* (Third ed., pp. 1303-1307). Philadelphia, PA: Lippincott Williams and Wilkins.

Kahn, S. E., & Porte, D. J. (2003). Chapter 21: The Pathophysiology and Genetics of Type 2 Diabetes Mellitus. In D. J. Porte, R. S. Sherwin & A. Baron (Eds.), *Ellenberg and Rifkin's Diabetes Mellitus* (6th ed.): McGraw-Hill.

Katon, W., & Felz-Cornelis, C. v. d. (2010). Treatment of depression in patients with diabetes: Efficacy, effectiveness and maintenance trials, and new service models *Depression and Diabetes* (pp. 81-107). Chichester, West Sussex: Wiley-Blackwell.

Katon, W., Von Korff, M., Lin, E., Simon, G., Walker, E., Unutzer, J., . . . Ludman, E. (1999). Stepped collaborative care for primary care patients with persistent symptoms of depression: a randomized trial. *Archives of General Psychiatry, 56*(12), 1109.

Katon, W., Von Korff, M., Lin, E., Walker, E., Simon, G. E., Bush, T., . . . Russo, J. (1995). Collaborative management to achieve treatment guidelines. Impact on depression in primary care. *JAMA: Journal of the American Medical Association, 273*(13), 1026-1031.

Katon, W. J., & Seelig, M. (2008). Population-based care of depression: team care approaches to improving outcomes. *Journal of Occupational and Environmental Medicine, 50*(4), 459-467.

Katon, W. J., Von Korff, M., Lin, E. H., Simon, G., Ludman, E., Russo, J., . . . Bush, T. (2004). The Pathways Study: a randomized trial of collaborative care in patients with diabetes and depression. *Archives of General Psychiatry, 61*(10), 1042.

Kauffman, R. P., Castracane, V. D., White, D. L., Baldock, S. D., & Owens, R. (2005). Impact of the selective serotonin reuptake inhibitor citalopram on insulin sensitivity, leptin and basal cortisol secretion in depressed and non-depressed euglycemic women of reproductive age. *Gynecological Endocrinology, 21*(3), 129-137.

Kawakami, N., Takatsuka, N., Shimizu, H., & Ishibashi, H. (1999). Depressive symptoms and occurrence of type 2 diabetes among Japanese men. *Diabetes Care, 22*(7), 1071-1076.

Kessler, R. C., Chiu, W. T., Demler, O., & Walters, E. E. (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry, 62*(6), 617.

Kline, R. B. (2010). *Principles and practice of structural equation modeling* (3rd ed.). New York: Guilford press.

Knol, M., Twisk, J., Beekman, A., Heine, R., Snoek, F., & Pouwer, F. (2006). Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. *Diabetologia, 49*(5), 837-845.

Knowler, W. C., Barrett-Connor, E., Fowler, S. E., Hamman, R. F., Lachin, J. M., Walker, E. A., & Nathan, D. M. (2002). Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *The New England Journal of Medicine, 346*(6), 393-403.

Koppes, L. L., Dekker, J. M., Hendriks, H. F., Bouter, L. M., & Heine, R. J. (2005). Moderate Alcohol Consumption Lowers the Risk of Type 2 Diabetes A meta-analysis of prospective observational studies. *Diabetes Care, 28*(3), 719-725.

Kroenke, K., Spitzer, R. L., & Williams, J. B. (2001). The PHQ-9: Validity of a brief depression severity measure. *J Gen Intern Med, 16*(9), 606-613.

Kronish, I. M., Rieckmann, N., Burg, M. M., Edmondson, D., Schwartz, J. E., & Davidson, K. W. (2012). The effect of enhanced depression care on adherence to risk-reducing behaviors after acute coronary syndromes: findings from the COPES trial. *Am Heart J, 164*(4), 524-529. doi: 10.1016/j.ahj.2012.07.024

Lamers, F., Jonkers, C., Bosma, H., Knottnerus, J. A., & van Eijk, J. T. M. (2011). Treating depression in diabetes patients: does a nurse-administered minimal psychological intervention affect diabetes-specific quality of life and glycaemic control? A randomized controlled trial. *Journal of Advanced Nursing, 67*(4), 788-799.

Lebowitz, B. D., Pearson, J. L., Schneider, L. S., Reynolds III, C. F., Alexopoulos, G. S., Bruce, M. L., . . . Morrison, M. F. (1997). Diagnosis and treatment of depression in late life. Consensus statement update. *JAMA, 278*(14), 1186-1190.

Lee, P. W., Schulberg, H. C., Raue, P. J., & Kroenke, K. (2007). Concordance between the PHQ-9 and the HSCL-20 in depressed primary care patients. *Journal of Affective Disorders, 99*(1), 139-145.

Lin, E. H., Katon, W., Rutter, C., Simon, G. E., Ludman, E. J., Von Korff, M., . . . Kinder, L. (2006). Effects of enhanced depression treatment on diabetes self-care. *The Annals of Family Medicine, 4*(1), 46-53.

Lin, E. H., Katon, W., Von Korff, M., Rutter, C., Simon, G. E., Oliver, M., . . . Young, B. (2004). Relationship of depression and diabetes self-care, medication adherence, and preventive care. *Diabetes Care, 27*(9), 2154-2160.

Lloyd, C. E., Hermanns, N., Nouwen, A., Pouwer, F., Underwood, L., & Winkley, K. (2010). The epidemiology of depression and diabetes *Depression and Diabetes*. Oxford: Wiley-Blackwell.

Lustman, P. J., Clouse, R. E., Nix, B. D., Freedland, K. E., Rubin, E. H., McGill, J. B., . . . Hirsch, I. B. (2006). Sertraline for prevention of depression recurrence in diabetes mellitus: a randomized, double-blind, placebo-controlled trial. *Archives of General Psychiatry, 63*(5), 521.

Lustman, P. J., Freedland, K. E., Griffith, L. S., & Clouse, R. E. (2000). Fluoxetine for depression in diabetes: a randomized double-blind placebo-controlled trial. *Diabetes Care, 23*(5), 618-623.

Lustman, P. J., Griffith, L. S., Clouse, R. E., Freedland, K. E., Eisen, S. A., Rubin, E. H., . . . McGill, J. B. (1997). Effects of nortriptyline on depression and glycemic control in diabetes: results of a double-blind, placebo-controlled trial. *Psychosomatic Medicine, 59*(3), 241-250.

Lustman, P. J., Griffith, L. S., Freedland, K. E., Kissel, S. S., & Clouse, R. E. (1998). Cognitive behavior therapy for depression in type 2 diabetes mellitusA randomized, controlled trial. *Annals of Internal Medicine, 129*(8), 613-621.

Lustman, P. J., Penckofer, S. M., & Clouse, R. E. (2007). Recent advances in understanding depression in adults with diabetes. *Current Diabetes Reports, 7*(2), 114-122.

Lustman, P. J., Williams, M. M., Sayuk, G. S., Nix, B. D., & Clouse, R. E. (2007). Factors influencing glycemic control in type 2 diabetes during acute-and maintenance-phase treatment of major depressive disorder with bupropion. *Diabetes Care, 30*(3), 459-466.

Malik, V. S., Popkin, B. M., Bray, G. A., Després, J.-P., Willett, W. C., & Hu, F. B. (2010). Sugar-Sweetened Beverages and Risk of Metabolic Syndrome and Type 2 Diabetes: A meta-analysis. *Diabetes Care, 33*(11), 2477-2483. doi: 10.2337/dc10-1079

Marcus, M. D., Wing, R. R., Guare, J., Blair, E. H., & Jawad, A. (1992). Lifetime prevalence of major depression and its effect on treatment outcome in obese type II diabetic patients. *Diabetes Care, 15*(2), 253-255.

Mathers, C., Fat, D. M., & Boerma, J. (2008). *The Global Burden of Disease: 2004 update*: World Health Organization.

Mayfield, D., McLeod, G., & Hall, P. (1974). The CAGE questionnaire: Validation of a new alcoholism screening instrument. *The American Journal of Psychiatry*.

McDonald, C. J., Tierney, W. M., Overhage, J. M., Martin, D., & Wilson, G. (1992). The Regenstrief Medical Record System: 20 years of experience in hospitals, clinics, and neighborhood health centers. *MD computing: Computers in Medical Practice, 9*(4), 206.

Mezuk, B., Eaton, W. W., Albrecht, S., & Golden, S. H. (2008). Depression and type 2 diabetes over the lifespan. *Diabetes Care, 31*(12), 2383-2390.

Morrow, J. D., Frei, B., Longmire, A. W., Gaziano, J. M., Lynch, S. M., Shyr, Y., . . . Roberts, L. J. (1995). Increase in Circulating Products of Lipid Peroxidation (F2-Isoprostanes) in Smokers — Smoking as a Cause of Oxidative Damage. *New England Journal of Medicine, 332*(18), 1198-1203. doi: doi:10.1056/NEJM199505043321804

Mozaffarian, D., Kamineni, A., Carnethon, M., Djoussé, L., Mukamal, K. J., & Siscovick, D. (2009). Lifestyle risk factors and new-onset diabetes mellitus in older adults: the cardiovascular health study. *Archives of Internal Medicine, 169*(8), 798.

Nouwen, A., Nefs, G., Caramlau, I., Connock, M., Winkley, K., Lloyd, C. E., . . . Pouwer, F. (2011). Prevalence of Depression in Individuals With Impaired Glucose Metabolism or Undiagnosed Diabetes A systematic review and meta-analysis of the European Depression in Diabetes (EDID) Research Consortium. *Diabetes Care, 34*(3), 752-762.

O'Connor, M., Butcher, I., Hansen, C. H., Kleiboer, A., Murray, G., Sharma, N., . . . Sharpe, M. (2010). Measuring improvement in depression in cancer patients: a 50% drop on the self-rated SCL-20 compared with a diagnostic interview. *General Hospital Psychiatry, 32*(3), 334-336.

Okamura, F., Tashiro, A., Utumi, A., Imai, T., Suchi, T., Tamura, D., . . . Hongo, M. (2000). Insulin resistance in patients with depression and its changes during the clinical course of depression: minimal model analysis. *Metabolism, 49*(10), 1255-1260.

Otte, C., Marmar, C. R., Pipkin, S. S., Moos, R., Browner, W. S., & Whooley, M. A. (2004). Depression and 24-hour urinary cortisol in medical outpatients with coronary heart disease: the Heart and Soul Study. *Biological Psychiatry, 56*(4), 241-247.

Overhage, J., McDonald, C. J., & Suico, J. G. (2000). *The regenstrief medical record system 2000: Expanding the breadth and depth of a community wide EMR.* Paper presented at the Proceedings of the AMIA Symposium.

Piette, J. D., Richardson, C., Himle, J., Duffy, S., Torres, T., Vogel, M., . . . Valenstein, M. (2011). A randomized trial of telephone counseling plus walking for depressed diabetes patients. *Medical Care, 49*(7), 641.

Platt, R., & Ommaya, A. (2005). A beneficial side effect of the Medicare drug benefit. *New England Journal of Medicine, 353*(26), 2742-2743.

Pratley, R. (2006). Islet dysfunction: an underlying defect in the pathophysiology of type 2 diabetes. *Endocrinology and Metabolism Clinics of North America, 35*, 6.

Pratt, L. A., & Brody, D. J. (2008). Depression in the United States Household Population, 2005-2006. *U.S. Department of Health and Human Services, Centers for Disease Control and Prevention*.

Preacher, K., & Hayes, A. (2008). Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. *Behavior Research Methods, 40*(3), 879-891. doi: 10.3758/BRM.40.3.879

Ray, W. A. (1997). Policy and program analysis using administrative databases. *Annals of Internal Medicine, 127*(8_Part_2), 712-718.

Roose, S. P., Glassman, A., Mathew, S. J., Musselman, D. L., Nelson, J. C., & Steffens, D. C. (2006). Academic Highlights: managing patients with vascular disease and depression. *Journal of Clinical Psychiatry, 67*(10), 1644-1644.

Rost, K., Nutting, P., Smith, J. L., Elliott, C. E., & Miriam Dickinson. (2002). Managing depression as a chronic disease: a randomised trial of ongoing treatment in primary care. *BMJ, 325*(7370), 934. doi: 10.1136/bmj.325.7370.934

Rustad, J. K., Musselman, D. L., & Nemeroff, C. B. (2011). The relationship of depression and diabetes: pathophysiological and treatment implications. *Psychoneuroendocrinology*.

Sacks, D. B., Arnold, M., Bakris, G. L., Bruns, D. E., Horvath, A. R., Kirkman, M. S., . . . Nathan, D. M. (2011). Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. *Clinical Chemistry, 57*(6), e1-e47.

Simon, G. E. (2002). Evidence review: efficacy and effectiveness of antidepressant treatment in primary care. *General Hospital Psychiatry, 24*(4), 213-224.

Singh, R., & Mukhopadhyay, K. (2011). Survival analysis in clinical trials: Basics and must know areas. *Perspectives in Clinical Research, 2*(4), 145.

Spector, T. D., & Blake, D. R. Effect Of Cigarette Smoking On Langerhans' Cells. *The Lancet, 332*(8618), 1028. doi: 10.1016/S0140-6736(88)90794-5

Spitzer, R. L., Williams, J. B., Kroenke, K., Linzer, M., Hahn, S. R., Brody, D., & Johnson, J. G. (1994). Utility of a new procedure for diagnosing mental disorders in primary care. The PRIME-MD 1000 Study. *JAMA: Journal of the American Medical Association, 272*(22), 1749-1756.

Stewart, P. (2008). The adrenal cortex *Williams Textbook of Endocrinology* (11th ed.). USA: Saunders/Elesevier.

Strine, T. W., Mokdad, A. H., Dube, S. R., Balluz, L. S., Gonzalez, O., Berry, J. T., . . . Kroenke, K. (2008). The association of depression and anxiety with obesity and unhealthy behaviors among community-dwelling US adults. *General Hospital Psychiatry, 30*(2), 127-137.

Stuart, M. J., & Baune, B. T. (2012). Depression and type 2 diabetes: inflammatory mechanisms of a psychoneuroendocrine co-morbidity. *Neuroscience & Biobehavioral Reviews, 36*(1), 658-676.

Stumvoll, M., Goldstein, B. J., & van Haeften, T. W. (2005). Type 2 diabetes: principles of pathogenesis and therapy. *The Lancet, 365*(9467), 1333-1346.

Talbot, F., & Nouwen, A. (2000). A review of the relationship between depression and diabetes in adults: is there a link? *Diabetes Care, 23*(10), 1556-1562.

Unutzer, J. (1999). The Impact Study Investigators: IMPACT Intervention Manual. Los Angeles, CA: Center for Health Services Research, UCLA Neuropsychiatric Institute.

Unützer, J., Choi, Y., Cook, I. A., & Oishi, S. (2002). Clinical computing: a web-based data management system to improve care for depression in a multicenter clinical trial. *Psychiatric Services, 53*(6), 671-678.

Unützer, J., Katon, W., Callahan, C. M., Williams Jr, J. W., Hunkeler, E., Harpole, L., . . . Lin, E. H. (2002). Collaborative care management of late-life depression in the primary care setting. *JAMA: Journal of the American Medical Association, 288*(22), 2836-2845.

Unützer, J., Katon, W., Williams Jr, J. W., Callahan, C. M., Harpole, L., Hunkeler, E. M., . . . Schoenbaum, M. (2001). Improving primary care for depression in late life: the design of a multicenter randomized trial. *Medical Care, 39*(8), 785-799.

van Bastelaar, K. M., Pouwer, F., Cuijpers, P., Riper, H., & Snoek, F. J. (2011). Web-Based Depression Treatment for Type 1 and Type 2 Diabetic Patients A randomized, controlled trial. *Diabetes Care, 34*(2), 320-325.

Van der Feltz-Cornelis, C. M., Nuyen, J., Stoop, C., Chan, J., Jacobson, A. M., Katon, W., . . . Sartorius, N. (2010). Effect of interventions for major depressive disorder and significant depressive symptoms in patients with diabetes mellitus: a systematic review and meta-analysis. *General Hospital Psychiatry, 32*(4), 380-395.

Voight, B. F., Scott, L. J., Steinthorsdottir, V., Morris, A. P., Dina, C., Welch, R. P., . . . Thorleifsson, G. (2010). Twelve type 2 diabetes susceptibility loci identified through large-scale association analysis. *Nature genetics, 42*(7), 579-589.

Vreeburg, S. A., Hoogendijk, W. J., van Pelt, J., DeRijk, R. H., Verhagen, J., van Dyck, R., . . . Penninx, B. W. (2009). Major depressive disorder and hypothalamic-pituitary-adrenal axis activity: results from a large cohort study. *Archives of General Psychiatry, 66*(6), 617.

Wagner, J., Allen, N. A., Swalley, L. M., Melkus, G. D., & Whittemore, R. (2009). Depression, depression treatment, and insulin sensitivity in adults at risk for type 2 diabetes. *Diabetes Research and Clinical Practice, 86*(2), 96-103.

Weber-Hamann, B., Gilles, M., Lederbogen, F., Heuser, I., & Deuschle, M. (2006). Improved insulin sensitivity in 80 nondiabetic patients with MDD after clinical remission in a double-blind, randomized trial of amitriptyline and paroxetine. *Journal of Clinical Psychiatry, 67*(12), 1856-1861.

Weber-Hamann, B., Gilles, M., Schilling, C., Onken, V., Frankhauser, P., Kopf, D., . . . Deuschle, M. (2008). Improved insulin sensitivity in 51 nondiabetic depressed inpatients remitting during antidepressive treatment with mirtazapine and venlafaxine. *Journal of Clinical Psychopharmacology, 28*(5), 581-584.

Weir, G. C., & Halban, P. A. (2001). Islet Cell Hormones: Production and Degradation. In K. L. Becker (Ed.), *Principles and Practices of Endrocrinology and Metabolism* (3rd ed., pp. 1296-1303). Philadelphia, PA: Lippincott Williams and Wilkins.

Wheatcroft, S., Williams, I., Shah, A., & Kearney, M. (2003). Pathophysiological implications of insulin resistance on vascular endothelial function. *Diabetic Medicine, 20*(4), 255-268.

Wilchesky, M., Tamblyn, R. M., & Huang, A. (2004). Validation of diagnostic codes within medical services claims. *Journal of Clinical Epidemiology, 57*(2), 131-141. doi: http://dx.doi.org/10.1016/S0895-4356(03)00246-4

Williams, J., John W., Stellato, C. P., Cornell, J., & Barrett, J. E. (2004). The 13-and 20-item Hopkins Symptom Checklist Depression Scale: psychometric properties in primary care patients with minor depression or dysthymia. *The International Journal of Psychiatry in Medicine, 34*(1), 37-50.

Williams Jr, J. W., Barrett, J., Oxman, T., Frank, E., Katon, W., Sullivan, M., . . . Sengupta, A. (2000). Treatment of dysthymia and minor depression in primary care. *Journal of the American Medical Association, 284*(12), 1519-1526.

Williams Jr, J. W., Pignone, M., Ramirez, G., & Perez Stellato, C. (2002). Identifying depression in primary care: a literature synthesis of case-finding instruments. *General Hospital Psychiatry, 24*(4), 225-237.

Williams, J. W., Jr., Katon, W., Lin, E. H., Noel, P. H., Worchel, J., Cornell, J., . . . Unutzer, J. (2004). The effectiveness of depression care management on diabetes-related outcomes in older patients. *Ann Intern Med, 140*(12), 1015-1024.

Zimmet, P., Alberti, K., & Shaw, J. (2001). Global and societal implications of the diabetes epidemic. *Nature, 414*(6865), 782-787.

TABLES

Table 1. Indicators, Data Sources, and Frequencies for the Baseline Diabetes Variables (N=235)

Baseline Variables	Indicators	Data Sources	Frequency
1. Diabetes Diagnoses	a) ICD-9 Diabetes Codes: • "Hospital ICD-9 diagnosis" contains: • "Admitting ICD-9 diagnosis" contains: • "Primary care diagnosis" contains: • "Clinic billing diagnosis" contains: • 250.XX	• Regenstrief Medical Records System • Medicare Inpatient Standard Analytic file • Medicare Outpatient Standard Analytic file • Medicare Carrier Standard Analytic File • Medicare Home Health Agency Standard Analytic File • Medicare Hospice Standard Analytic File • Medicare Skilled Nursing Standard Analytic File • Indiana Medicaid Claims	94 (40%)
	b) Diabetes Diagnosis Text Field Phrases: • V "diabetes mel non insulin dep" • V "diabetes mel insulin dep" • V "diabetes out of control" • V "diabetes uncontrolled	• Regenstrief Medical Records System	40 (17.0%)
2. Diabetes Complications	Diabetes Complications Text Field Phrases: • V "diabetic ketoacidos" • V "diabetic neuropathy" • V "diabetic retinopathy" • V "diab hyperosm coma adult" • V "diab nephropathy adlt controlled" • V "diab nephropathy adlt uncontroll" • V "diab nephropathy juv controlled" • V "diab nephropathy juv uncontroll" • V "diabetic enteropathy" • V "diabetic foot ulcer" • V "diabetic lipodystrophy" • V "background diabetic retinopathy" • V "pre prolif diabetic retinopathy" • V "proliferatv diabetic retinopathy"	• Regenstrief Medical Records System	22 (9.4%)

Table 1 continued. Indicators, Data Sources, and Frequencies for the Baseline Diabetes Variables (N=235)

Baseline Variables	Indicators	Data Sources	Frequency
2. Diabetes Complications (contd.)	• V "diabetic skin ulcer"		
3. Diabetes Laboratory Values	a) Fasting Glucose Values: • "Glu Fasting" ≥ 126 • "Gluc-GTT-75gm-Fast" ≥ 126	• Regenstrief Medical Records System	58 (24.7%)
	b) HbA_{1c} Values: • "Glycosylated HGB tests" ≥ 8.5% • "HGB A1C-calculated" ≥ 8.5%	• Regenstrief Medical Records System	65 (27.7%)
4. Diabetes Medications	a) Insulin Prescription: • "Insulins" • "Insulin Hum 70/30" • "Humulin 50/50" • "Insulin Lispro" • "Insulin Pen" • "Insulin SS Hum R" • "Insulin Drip"	• Regenstrief Medical Records System • Medicare, Part D	33 (14.0%)
	b) Prescription for Oral Hypoglycemic Medications: • Glyburide • Glyburide Prestab • Glipizide • Glipizide Xl • Glimepiride • Gliquidone • Glyclopyramide • Gliclazide • Rosiglitazone • Pioglitazone	• Regenstrief Medical Records System • Medicare, Part D	26 (11.1%)

Table 1 continued. Indicators, Data Sources, and Frequencies for the Baseline Diabetes Variables (N=235)

Baseline Variables	Indicators	Data Sources	Frequency
4. Diabetes Medications (contd.)	b) Prescription for Oral Hypoglycemic Medications: • Troglitazone • Acarbose • Miglitol • Repaglinide • Nateglinide • Exenatide • Pramlintide • Liraglutide • Tolbutamide • Tolazamide • Chlorpropamide • Acetohexamide • Saxagliptin • Linagliptin • Vildagliptin • Alogliptin • Sitagliptin • Dapagliflozin • Canagliflozin	• Regenstrief Medical Records System • Medicare, Part D	26 (11.1%)
5. Self-reported Diabetes	Self-report Question Assessing Diabetes Status: • "Has a doctor or another health care worker diagnosed you with or treated you for high blood sugar or diabetes in the past 3 years?"	• IMPACT baseline structured interview	86 (36.6%)

Note. *N* = 235. ICD-9 = International Classification of Diseases-9th Revision. HbA_{1c} = Hemoglobin A_{1c}

Table 2. Indicators, Data Sources, and Frequencies for the Incident Diabetes Variables (N=160)

Outcome Variables	Indicator	Data Sources	Frequency
1. Diabetes Diagnoses	a) ICD-9 Diabetes Codes: • "Hospital ICD-9 diagnosis" contains: • "Admitting ICD-9 diagnosis " contains: • "Primary care diagnosis " contains: • "Clinic billing diagnosis " contains: • 250.XX	• Regenstrief Medical Records System • Medicare Inpatient Standard Analytic file • Medicare Outpatient Standard Analytic file • Medicare Carrier Standard Analytic File • Medicare Home Health Agency Standard Analytic File • Medicare Hospice Standard Analytic File • Medicare Skilled Nursing Standard Analytic File • Indiana Medicaid Claims	46 (28.8%)
	b) Diabetes Diagnosis Text Field Phrases: • V "diabetes mel non insulin dep" • V "diabetes mel insulin dep" • V "diabetes out of control" • V "diabetes uncontrolled"	• Regenstrief Medical Records System	7 (4.4%)
2. Diabetes Complications	Diabetes Complications Text Field Phrases: • V "diabetic ketoacidos" • V "diabetic neuropathy" • V "diabetic retinopathy" • V "diab hyperosm coma adult" • V "diab nephropathy adlt controlled" • V "diab nephropathy adlt uncontroll" • V "diabetic enteropathy" • V "diabetic foot ulcer" • V "diabetic lipodystrophy" • V "background diabetic retinopathy" • V "pre prolif diabetic retinopathy" • V "proliferatv diabetic retinopathy" • V "diabetic skin ulcer"	• Regenstrief Medical Records System	7 (4.4%)

Table 2 continued. Indicators, Data Sources, and Frequencies for the Incident Diabetes Variables (N=160)

Outcome Variables	Indicator	Data Sources	Frequency
3. Diabetes Laboratory Values	a) Fasting Glucose Values: • "Glu fasting" ≥ 126 • "Gluc-GTT-75gm-fast" ≥ 126	• Regenstrief Medical Records System	51 (31.9%)
	b) HbA_{1c} Values: • "Glycosylated HGB tests" ≥ 8.5% • "HGB A1C-calculated" ≥ 8.5%	• Regenstrief Medical Records System	13 (8.1%)
4. Diabetes Medications	a) Insulin Prescription: • "Insulins" • "Insulin Hum 70/30" • "Humulin 50/50" • "Insulin Lispro" • "Insulin Pen" • "Insulin SS Hum R" • "Insulin Drip"	• Regenstrief Medical Records System • Medicare, Part D	6 (3.8%)
	b) Prescription for Oral Hypoglycemic Medications: • Glyburide • Glyburide Prestab • Glipizide • Glipizide Xl • Glimepiride • Gliquidone • Glyclopyramide • Gliclazide • Rosiglitazone • Pioglitazone • Troglitazone • Acarbose • Miglitol • Repaglinide	• Regenstrief Medical Records System • Medicare, Part D	13 (8.1%)

Table 2 continued. Indicators, Data Sources, and Frequencies for the Incident Diabetes Variables (N=160)

Outcome Variables	Indicator	Data Sources	Frequency
4. Diabetes Medications (contd.)	b) Prescription for Oral Hypoglycemic Medications: • Nateglinide • Exenatide • Pramlintide • Liraglutide • Tolbutamide • Tolazamide • Chlorpropamide • Acetohexamide • Saxagliptin • Linagliptin • Vildagliptin • Alogliptin • Sitagliptin • Dapagliflozin • Canagliflozin	• Regenstrief Medical Records System • Medicare, Part D	13 (8.1%)

Note. *N* = 160. ICD-9 = International Classification of Diseases-9th Revision. HbA_{1c} = Hemoglobin A_{1c}

Table 3. Characteristics of Participants by Treatment Group

Characteristic	**IMPACT (*n* = 80)**	**Usual Care (*n* = 80)**	***p* value**
Baseline Demographic Factors			
Age, mean (SD)	66.9 (6.8)	67.6 (6.9)	.514
Male, %	20.0	26.3	.348
African-American†, %	41.3	47.5	.426
Height (inches), mean (SD)	64.6 (3.1)	65.1 (3.8)	.363
Weight (pounds), mean (SD)	184.2 (53.5)	175.7 (54.6)	.320
Baseline Diabetes Risk Factors			
Hypertension, %	72.5	72.5	1.000
Smoker, %	31.3	40.0	.248
Body-Mass Index (kg/m^2), mean (SD)	31.1 (8.9)	29.1 (8.3)	.137
Baseline Depression Variables			
MDD Only, %	13.8	10.0	.463
Dysthymia Only, %	32.5	37.5	.507
MDD and Dysthymia, %	53.8	52.5	.874
SCL-20 Score, mean (SD) (range: 0-4)	1.4 (0.5)	1.5 (0.5)	.074
Antidepressant Use in Past 3 Months, %	56.3	47.5	.268
Depression Outcomes and Care Variables			
SCL-20 Change, mean (SD) (*N* = 152)	-0.3 (0.7)	0.0 (0.7)	.013
Antidepressants during the trial, %	73.8	65.0	.230
Psychotherapy during the trial, %	61.3	21.3	<.001

Note. *N* = 160 except where indicated. Independent samples *t* tests were used to compare groups on age, body mass index, baseline SCL-20 score, and SCL-20 change. All other group comparisons were made using chi-square tests. IMPACT = Improving Mood-Promoting Access to Collaborative Treatment. MDD = major depressive disorder. SCL-20 = Symptom Checklist-20.

†Because only 5 (3%) patients and 4 (2%) patients fell into the Hispanic and Other categories, respectively, a dichotomous race/ethnicity variable (0 = White, Hispanic, and Other; 1 = African American) was created

Table 4. Event Composition of the Primary Definition of Incident Diabetes by Treatment Group

Events	**Total Sample (N = 160)**	**IMPACT (*n* = 80)**	**Usual Care (*n* = 80)**
Total Events	33	22	11
Composition of Events			
ICD-9 Code and Positive Fasting Glucose	16 (49%)	11(50%)	5 (46%)
ICD-9 Code and Positive HbA_{1c}	10 (30%)	8 (36%)	2 (18%)
ICD-9 Code and Diabetes Medication	7 (21%)	3 (14%)	4 (36%)

Note. ICD-9 = International Classification of Diseases-9th Revision. IMPACT = Improving Mood-Promoting Access to Collaborative Treatment. HbA_{1c} = Hemoglobin A_{1c}

Table 5. Results of Cox Proportional Hazard Regression Models Examining Treatment Group as a Predictor of Incident Diabetes

Diabetes Outcome	**Total Sample (N = 160)**	**IMPACT (*n* = 80)**	**Usual Care (*n* = 80)**	**Treatment Group (IMPACT vs. Usual Care)**		
		Events (%)		***HR***	**95% *CI***	***p* value**
Primary Definition ‖	33 (20.6%)	22 (27.5%)	11 (13.7%)	1.94	0.93-4.02	.076
Demographics Adjusted †				1.94	0.93-4.05	.075
Diabetes Risk Factors Adjusted ‡				1.73	0.81-3.68	.157
Secondary Definition §	67 (41.9%)	37 (46.2%)	30 (37.5%)	1.23	0.76-1.99	.399
Demographics Adjusted †				1.20	0.74-1.96	.454
Diabetes Risk Factors Adjusted ‡				1.11	0.68-1.82	.669
ICD-9 Code Only *	46 (28.8%)	26 (32.5%)	20 (25.0%)	1.24	0.69-2.23	.476
Demographics Adjusted †				1.23	0.68-2.22	.499
Diabetes Risk Factors Adjusted ‡				1.09	0.59-2.00	.781
Fasting Glucose Values Only ¶	51 (31.9%)	31 (38.7%)	20 (25.0%)	1.57	0.89-2.75	.117
Demographics Adjusted †				1.53	0.87-2.69	.141
Diabetes Risk Factors Adjusted ‡				1.42	0.80-2.52	.231

Table 5 continued. Results of Cox Proportional Hazard Regression Models Examining Treatment Group as a Predictor of Incident Diabetes

Diabetes Outcome	Total Sample (N = 160)	IMPACT (*n* = 80)	Usual Care (*n* = 80)	Treatment Group (IMPACT vs. Usual Care)		
		Events (%)		*HR*	95% *CI*	*p* value
HbA_{1c} Only ǂ	13 (8.1%)	9 (11.2%)	4 (5.0%)	2.15	0.66-7.00	.202
Demographics Adjusted †				2.12	0.65-6.98	.215
Diabetes Risk Factors Adjusted ‡				1.65	0.47-5.75	.429
Diabetes Medication Only ±	19 (11.9%)	11 (13.7%)	8 (10.0%)	1.33	0.53-3.31	.539
Demographics Adjusted †				1.44	0.57-3.61	.443
Diabetes Risk Factors Adjusted ‡				1.25	0.48-3.28	.651

Note. *N* = 160. *HR* = hazard ratio. *CI* = confidence interval. ICD-9 = International Classification of Diseases-9th Revision. IMPACT = Improving Mood-Promoting Access to Collaborative Treatment. HbA_{1c} = Hemoglobin A_{1c}

ǁ Defined as [ICD-9 code AND (fasting glucose OR HbA_{1c} OR diabetes medication)].

† Adjusted for age, sex, and race/ethnicity.

‡ Adjusted for age, sex, race/ethnicity, hypertension, smoking status, and body mass index. Body mass index was an independent predictor of incident diabetes in the expected direction (*HR* = 1.08, 95% *CI*: 1.04-1.12, $p < .001$).

§ Defined as (ICD-9 code OR fasting glucose OR HbA_{1c} OR diabetes medication).

* Defined as an ICD-9 code for diabetes.

ϯ Defined as a fasting glucose value ≥ 126mg/dL.

ǂ Defined as an HbA_{1c} value ≥ 8.5%.

± Defined as a prescription for diabetes medication (insulin or oral hypoglycemic medication).

Table 6. Results of Cox Proportional Hazard Regression Models Examining Treatment Group as a Predictor of Incident Diabetes – Broad Baseline Definition

Diabetes Outcome	**Total Sample (N = 120)**	**IMPACT (*n* = 60)**	**Usual Care (*n* = 60)**	**Treatment Group (IMPACT vs. Usual Care)**		
		Events (%)		***HR***	**95% *CI***	***p* value**
Primary Definition ‖	16 (13.3%)	12 (20.0%)	4 (6.7%)	2.76	0.88-8.66	.083
Demographics Adjusted †				3.27	1.03-10.35	.044
Diabetes Risk Factors Adjusted ‡				2.25	0.65-7.84	.201
Secondary Definition §	40 (33.3%)	23 (38.3%)	17 (28.3%)	1.35	0.72-2.53	.348
Demographics Adjusted †				1.38	0.73-2.60	.322
Diabetes Risk Factors Adjusted ‡				1.24	0.64-2.38	.521
ICD-9 Code Only *	21 (17.5%)	14 (23.3)	7 (11.7%)	1.90	0.76-4.76	.171
Demographics Adjusted †				2.07	0.82-5.25	.126
Diabetes Risk Factors Adjusted ‡				1.80	0.68-4.76	.237
Fasting Glucose Values Only ☨	34 (28.3%)	20 (33.3%)	14 (23.3%)	1.36	0.86-2.69	.382
Demographics Adjusted †				1.40	0.70-2.78	.341
Diabetes Risk Factors Adjusted ‡				1.17	0.57-2.37	.672

Table 6 continued. Results of Cox Proportional Hazard Regression Models Examining Treatment Group as a Predictor of Incident Diabetes – Broad Baseline Definition

Diabetes Outcome	Total Sample (N = 120)	IMPACT (*n* = 60)	Usual Care (*n* = 60)	Treatment Group (IMPACT vs. Usual Care)		
		Events (%)		*HR*	95% *CI*	*p* value
HbA_{1c} Only ǂ	6 (5.0%)	6 (5.0%)	0 (0.0%)	60.7	0.08-45482.82	.224
Demographics Adjusted †				---	---	---
Diabetes Risk Factors Adjusted ‡				---	---	---
Diabetes Medication Only ±	7 (5.8%)	5 (8.3%)	2 (3.3%)	2.56	0.50-13.17	.262
Demographics Adjusted †				4.79	0.85-27.00	.076
Diabetes Risk Factors Adjusted ‡				5.62	0.67-47.28	.112

Note. *N* = 120. *HR* = hazard ratio. *CI* = confidence interval. ICD-9 = International Classification of Diseases-9th Revision. IMPACT = Improving Mood-Promoting Access to Collaborative Treatment. HbA_{1c} = Hemoglobin A_{1c}

‖ Defined as [ICD-9 code AND (fasting glucose OR HbA_{1c} OR diabetes medication)].

† Adjusted for age, sex, and race/ethnicity.

‡ Adjusted for age, sex, race/ethnicity, hypertension, smoking status, and body mass index. Body mass index was an independent predictor of incident diabetes in the expected direction (*HR* = 1.08, 95% *CI*: 1.04-1.12, $p < .001$).

§ Defined as (ICD-9 code OR fasting glucose OR HbA_{1c} OR diabetes medication).

* Defined as an ICD-9 code for diabetes.

ϯ Defined as a fasting glucose value ≥ 126mg/dL.

ǂ Defined as an HbA_{1c} value ≥ 8.5%.

Table 7. Results of Cox Proportional Hazard Regression Models Examining Treatment Group as a Predictor of Incident Diabetes - $HbA_{1c} \geq 8.0\%$

Diabetes Outcome	**Total Sample (N = 159)**	**IMPACT (*n* = 79)**	**Usual Care (*n* = 80)**	**Treatment Group (IMPACT vs. Usual Care)**		
		Events (%)		***HR***	**95% *CI***	***p* value**
Primary Definition ‖	33 (20.8%)	22 (27.8%)	11 (13.8%)	1.78	0.86-3.68	.118
Demographics Adjusted †				1.84	0.88-3.86	.105
Diabetes Risk Factors Adjusted ‡				1.68	0.78-3.63	.186
Secondary Definition §	66 (41.5%)	36 (45.6%)	30 (37.7%)	1.20	0.74-1.95	.458
Demographics Adjusted †				1.18	0.72-1.92	.510
Diabetes Risk Factors Adjusted ‡				1.09	0.67-1.79	.721
ICD-9 Code Only *	45 (28.3%)	20 (25.0%)	25 (31.6%)	1.19	0.66-2.16	.556
Demographics Adjusted †				1.19	0.65-2.16	.568
Diabetes Risk Factors Adjusted ‡				1.07	0.58-1.97	.837
Fasting Glucose Values Only ¶	51 (32.1%)	20 (25.0%)	31 (39.2%)	1.60	0.91-2.80	.102
Demographics Adjusted †				1.56	0.89-2.75	.120
Diabetes Risk Factors Adjusted ‡				1.47	0.83-2.60	.190

Table 7 continued. Results of Cox Proportional Hazard Regression Models Examining Treatment Group as a Predictor of Incident Diabetes - $HbA_{1c} \geq 8.0\%$

Diabetes Outcome	Total Sample (N = 160)	IMPACT (*n* = 80)	Usual Care (*n* = 80)	Treatment Group (IMPACT vs. Usual Care)		
		Events (%)		*HR*	95% *CI*	*p* value
HbA_{1c} Only ǂ	16 (10.1%)	10 (12.7%)	6 (7.5%)	1.62	0.59-4.44	.354
Demographics Adjusted †				1.62	0.58-4.50	.353
Diabetes Risk Factors Adjusted ‡				1.49	0.51-4.36	.467
Diabetes Medication Only ±	19 (11.9%)	11 (13.9%)	8 (10.0%)	1.35	0.54-3.36	.515
Demographics Adjusted †				1.47	0.58-3.68	.416
Diabetes Risk Factors Adjusted ‡				1.27	0.49-3.33	.622

Note. *N* = 159. *HR* = hazard ratio. *CI* = confidence interval. ICD-9 = International Classification of Diseases-9th Revision. IMPACT = Improving Mood-Promoting Access to Collaborative Treatment. HbA_{1c} = Hemoglobin A_{1c}

ǁ Defined as [ICD-9 code AND (fasting glucose OR HbA_{1c} OR diabetes medication)].

† Adjusted for age, sex, and race/ethnicity.

‡ Adjusted for age, sex, race/ethnicity, hypertension, smoking status, and body mass index. Body mass index was an independent predictor of incident diabetes in the expected direction (*HR* = 1.08, 95% *CI*: 1.04-1.12, $p < .001$).

§ Defined as (ICD-9 code OR fasting glucose OR HbA_{1c} OR diabetes medication).

* Defined as an ICD-9 code for diabetes.

ϯ Defined as a fasting glucose value ≥ 126mg/dL.

ǂ Defined as an HbA_{1c} value ≥ 8.0%.

± Defined as a prescription for diabetes medication (insulin or oral hypoglycemic medication).

FIGURES

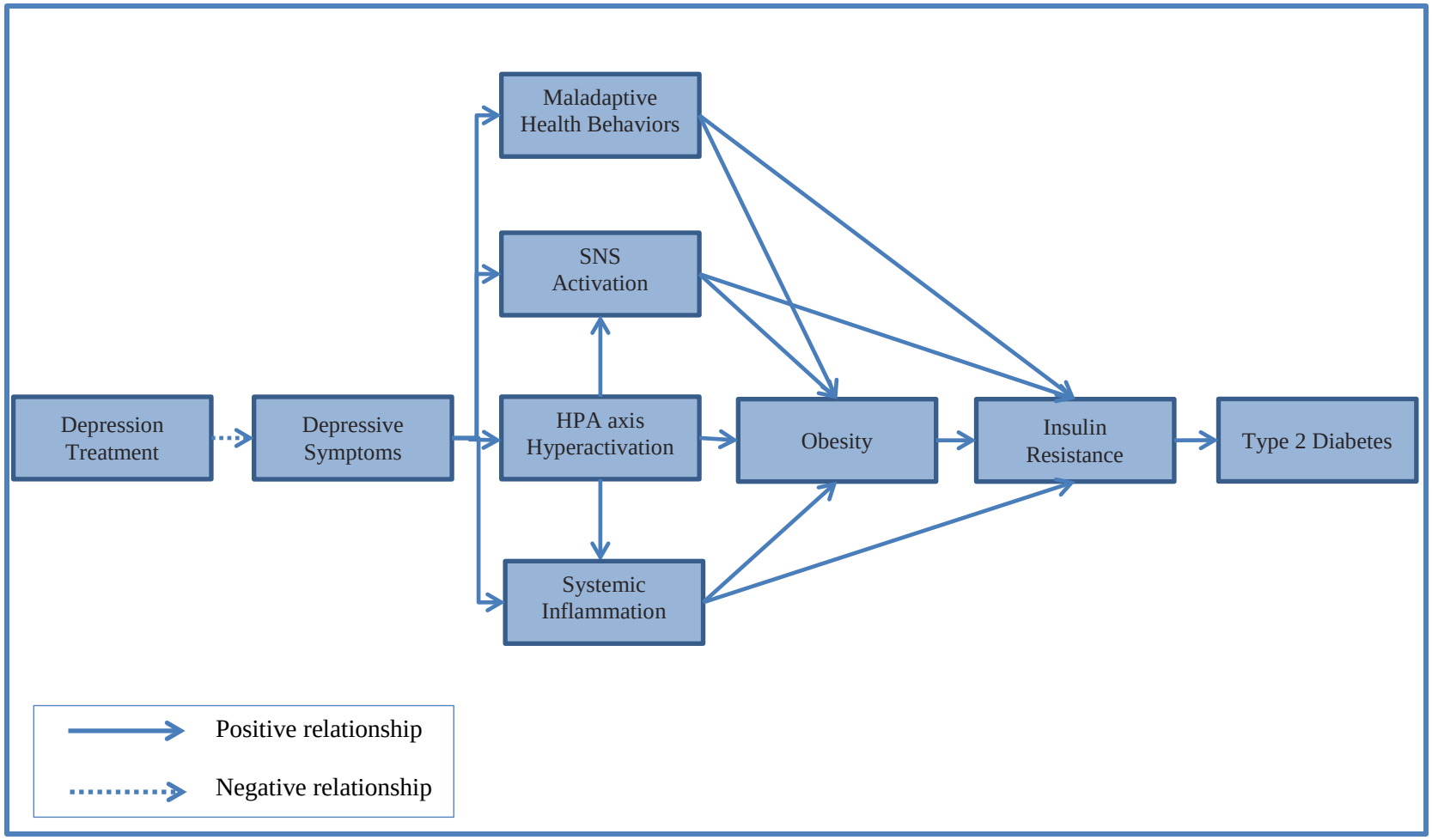

Figure 1. Hypothesized mechanisms underlying the prospective relationship between depression and diabetes.

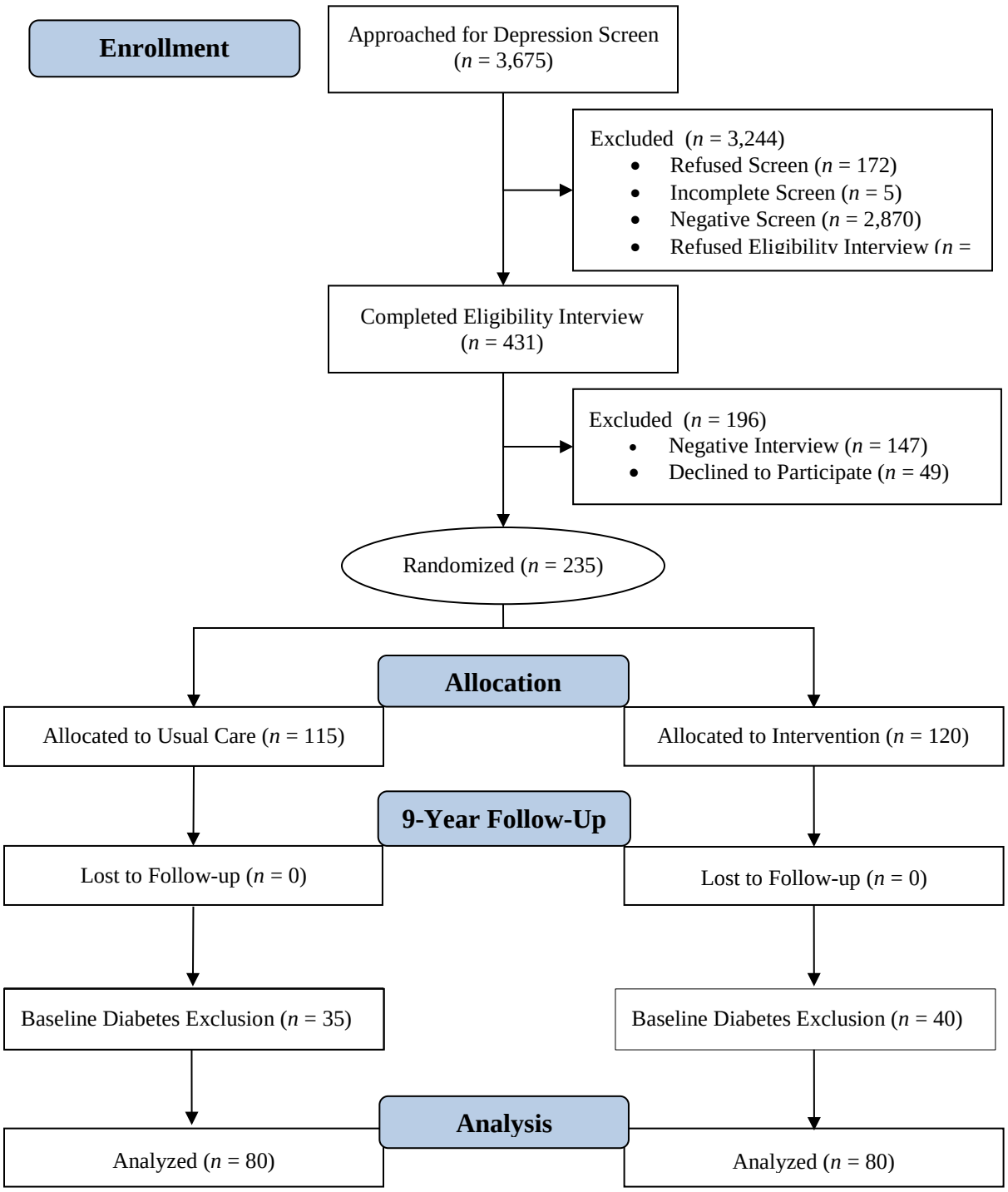

Figure 2. Flowchart of participants from the Indiana sites of the Improving Mood-Promoting Access to Collaborative Treatment (IMPACT) randomized controlled trial.

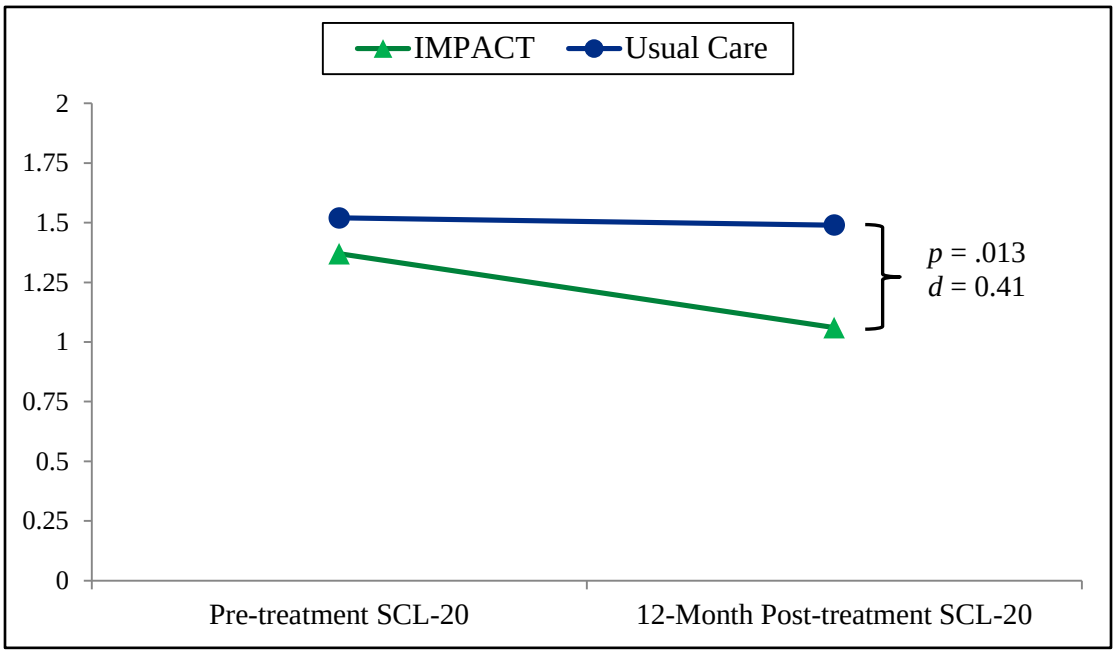

Figure 3. Change in depressive symptom severity (SCL-20) from pre-treatment to 12-month post-treatment for the IMPACT group (n = 80) and the usual care group (n = 80). SCL-20 = Symptom Checklist-20.

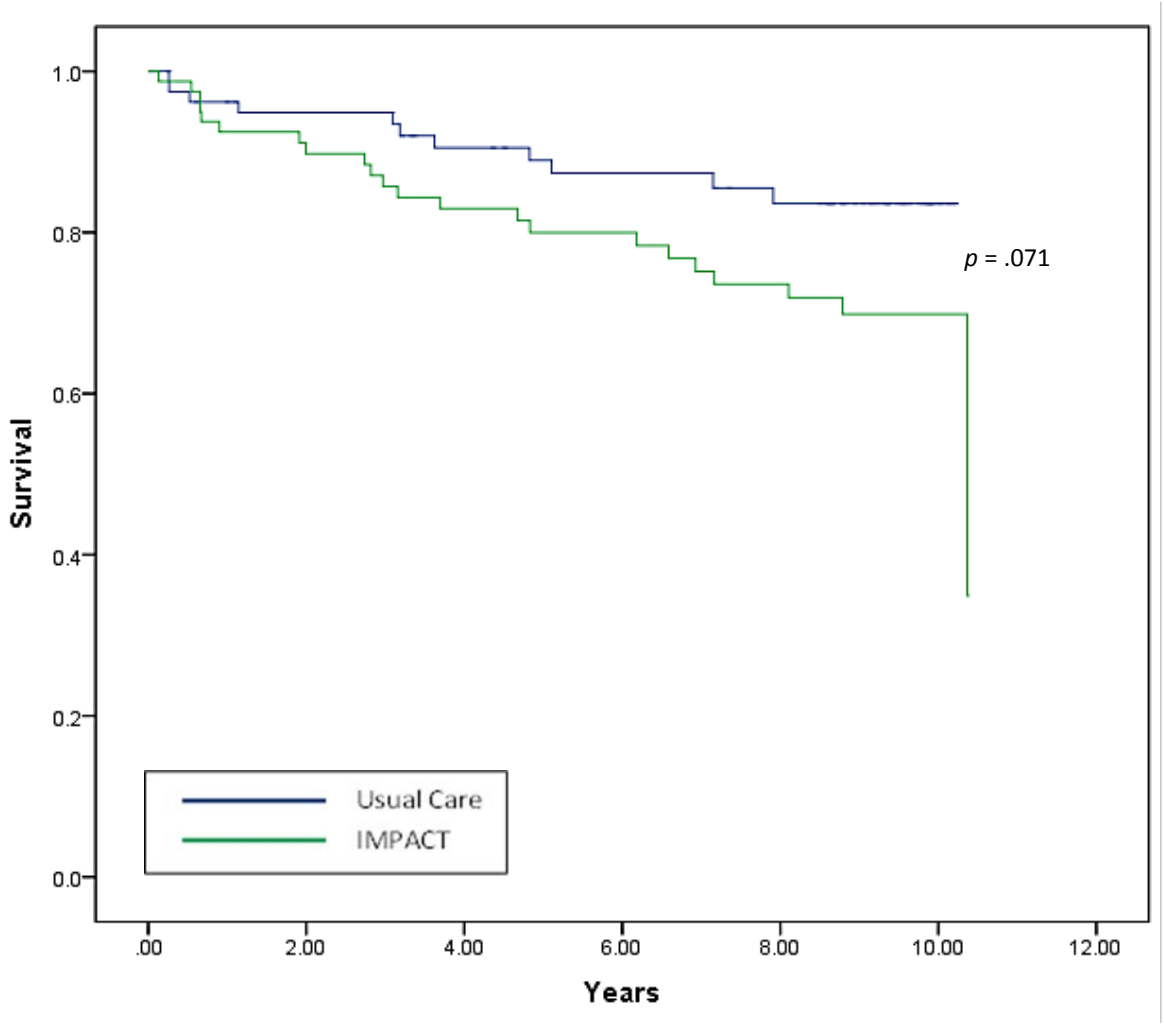

Figure 4. Kaplan-Meier survival curves for time to incident diabetes (ICD-9 diabetes code and positive laboratory value or diabetes medication use) among depressed patients initially free of diabetes. IMPACT = Improving Mood-Promoting Access to Collaborative Treatment.

VITA

VITA

TASNEEM KHAMBATY, PH.D.

Indiana University-Purdue University Indianapolis (IUPUI)

Department of Psychology

EDUCATION

August 2014 -	**Internship in Clinical Psychology (APA accredited)**
August 2015	Michael E. DeBakey VAMC, Houston, TX
Training Director:	Ellen Teng, PhD
May 2012 -	**PhD Candidate in Clinical Psychology (APA accredited)**
May 2015	Indiana University-Purdue University Indianapolis (IUPUI), Indianapolis, IN
Specialization:	Health Psychology
Advisor:	Jesse C. Stewart, PhD
Dissertation:	Depression Treatment and Diabetes Risk: A 9-Year Follow-Up Study of the IMPACT Trial
Defended:	February 10, 2015

Preliminary Examination: Possible Roles of Psychological Distress in Periodontal Disease: Antecedent, Consequence, Epiphenomenon, or Moderator? (Systematic review)

Defended: December 18, 2012

August 2009 - May 2012 **Masters of Science in Clinical Psychology (APA accredited)**

Indianapolis, IN Indiana University-Purdue University Indianapolis (IUPUI), Specialization: Health Psychology

Advisor: Jesse C. Stewart, PhD

Masters Thesis: Is Periodontal Disease a Partial Mediator of the Association between Depressive Symptoms and Cardiovascular Disease?

Defended: December 13, 2011

September 2005 - June 2009 **Bachelors of Science**

Ohio State University, Columbus OH

Magna Cum Laude

Major: Psychology; Minors: Neuroscience, Business

Honors Thesis: Variability in Daily Experiences of Mood and its Correlates

Chairperson: Daniel R. Strunk, PhD

Defended: May, 2009

AWARDS AND HONORS

May 2015 **Educational Enhancement Grant for Research Travel ($500)**

IUPUI Graduate Student Office

March 2015 **Clinical Psychology Travel Award ($650)**

IUPUI Department of Psychology

May 2014	**School of Science Travel Award ($400)**
	IUPUI Graduate Student Council
April 2014	**Clinical Psychology Award for Research, Honorable Mention**
	IUPUI Department of Psychology
April 2014	**Educational Enhancement Grant for Research Travel ($500)**
	IUPUI Graduate Student Office
December 2013	**Young Investigator Scholarship ($1,500)**
	Conference on Retroviruses and Opportunistic Infections 2014, Boston, MA
May 2013	**University Travel Fellowship ($800)**
	IUPUI School of Science
April 2012	**Doctoral Fellowship ($1,500)**
	Southern Regional Education Board, Institute on Teaching and Mentoring
March 2013	**Clinical Psychology Award for Citizenship ($100)**
	IUPUI Department of Psychology
February 2013	**Educational Enhancement Grant for Research Travel ($500)**
	IUPUI Graduate Student Office
January 2013	**Young Scholar Award ($500)**
	American Psychosomatic Society 2013, Miami, FL
February 2012	**Educational Enhancement Grant for Research Travel ($500)**
	IUPUI Graduate Student Office

December 2011	**Citation Abstract**
	Society of Behavioral Medicine 2012, New Orleans, LA
December 2011	**Meritorious Student Abstract**
	Society of Behavioral Medicine 2012, New Orleans, LA
April 2011	**Research Travel Award ($150)**
	IUPUI Department of Psychology
April 2011	**Poster Award Finalist**
	IUPUI Graduate Research Day
2006 – 2009	**Dean's List**
	College of the Arts and Sciences, Ohio State University

PEER-REVIEWED PUBLICATIONS

Khambaty, T., & Stewart, J. C. (2013). Associations of Depressive and Anxiety Disorders with Periodontal Disease Prevalence in Young Adults: Analysis of 1999–2004 National Health and Nutrition Examination Survey (NHANES) Data. *Annals of Behavioral Medicine*, 1-5.

Hickman, R. J., **Khambaty, T.**, & Stewart, J. C. (2013). C-Reactive Protein is Elevated in Atypical but not Nonatypical Depression: Data from the National Health and Nutrition Examination Survey (NHANES) 1999–2004. *Journal of Behavioral Medicine*, 1-9.

Khambaty, T., Stewart, J. C., Muldoon, M. F., & Kamarck, T. W. (2014). Depressive Symptom Clusters as Predictors of 6-Year Increases in Insulin Resistance: Data from the Pittsburgh Healthy Heart Project. *Psychosomatic Medicine*, 363-369.

Berntson, J., Stewart, K. R., Vrany, E., **Khambaty, T**., & Stewart, J. C. (2015). Depressive symptoms and self-reported adherence to medical recommendations to prevent cardiovascular disease: NHANES 2005–2010.*Social Science & Medicine*, *138*, 74-81.

Vrany, E., Berntson, J., **Khambaty, T.**, & Stewart, J. C. (in press). Somatic, but not Nonsomatic, Symptoms of Depression are Associated with Insulin Resistance: National Health and Nutrition Examination Survey (NHANES) 2005-2010. *Annals of Behavioral Medicine.*

MANUSCRUPTS UNDER REVIEW

Khambaty, T., Callahan C. M., & Stewart, J. C. Depression Treatment and Diabetes Risk: A 9-Year Follow-up Study of the IMPACT Trial.

Miles, S.R., **Khambaty, T.**, Peterson, N., Naik, A.D, & Cully, J.A. Knowledge Isn't Everything: The Role of Affect and Coping in Diabetes Care for Rural Adults with Uncontrolled Diabetes

Stewart, J.C., Hawkins, M.A.W., **Khambaty, T**., Perkins, A.J., & Callahan, C.M. Depression and Anxiety Screens as Predictors of 8-Year Incidence of Myocardial Infarction and Stroke in Primary Care Patients

White, J. R., Chang, C.H., So-Armah, K.A., Stewart, J.C., Gupta, S.K., Butt, A.A., Gibert, C.A., Rimland D., Rodriguez-Barradas, M.C., Leaf, D.A., Bedimo, R.J., Gottdiener, J.S., Kop, W.J., Gottlieb, S.S., Budoff, M.J**.**, **Khambaty, T**., Tindle, H., Justice, A.C., and Freiberg, M.S. (2014). Depression and HIV Infection are Risk Factors for Incident Heart Failure among Veterans: Veterans Aging Cohort Study.

MANUSCRIPTS IN PREPARATION

Khambaty, T., Stewart, J. C., Gupta, S. K., Chang, J., Bedimo R., Budoff, M., Butt, A., Crane, H., Gibert, C., Leaf, D., Rimland, D., Tindle, H., & Freiberg, M. S. Depressive Disorders Predict Incident Acute Myocardial Infarction in HIV+ Veterans: Veterans Aging Cohort Study.

Khambaty, T., Callahan, C.M., Perkins, A.J., & Stewart, J. C. Depression and Anxiety Screens as Predictors of 9-Year Incidence of Diabetes.

CONFERENCE PRESENTATIONS

Oral Presentations at National Meetings:

Khambaty, T., Callahan, C.M., Perkins, A.J., & Stewart, J. C. (2015, March). *Depression and Anxiety Screens as Predictors of 9-Year Incidence of Diabetes.* Paper presented at the 73nd Annual Scientific Meeting of the American Psychosomatic Society, Savannah, GA.

White, J. R., Chang, C.H., So-Armah, K.A., Stewart, J.C., Gupta, S.K., Butt, A.A., Gibert, C.A., Rimland D., Rodriguez-Barradas, M.C., Leaf D.A., Bedimo, R.J., Gottdiener J.S., Kop W.J., Gottlieb S.S., Budoff M.J**., Khambaty T**.; Tindle H., Justice A.C., and Freiberg M.S. (2014). *Antidepressant Use and Incident Heart Failure among Veterans with and without HIV Infection and Major Depressive Disorder.* Paper presented at 2015 American Heart Association Epidemiology & Prevention / Lifestyle and Cardiometabolic Health Scientific Sessions

Khambaty, T., & Stewart, J. C. (2014, March). *Atypical Major Depression is more Strongly Associated with Diabetes Prevalence Three Years Later than Nonatypical Depression and Dysthymia: National Epidemiologic Survey on Alcohol and Related Conditions (NESARC).* Paper presented at the 72nd Annual Scientific Meeting of the American Psychosomatic Society, San Francisco, CA.

White, J. R., Chang, C.H., So-Armah, K.A., Stewart, J.C., Gupta, S.K., Butt, A.A., Gibert, C.A., Rimland D., Rodriguez-Barradas, M.C., Leaf D.A., Bedimo, R.J., Gottdiener J.S., Kop W.J., Gottlieb S.S., Budoff M.J**., Khambaty T**.; Tindle H., Justice A.C., and Freiberg M.S. (2014). *Depression and HIV Infection are Risk Factors for Incident Heart Failure among Veterans: Veterans Aging Cohort Study*. Paper presented at the 2014 Annual Meeting of the Conference on Retroviruses and Opportunistic Infections, Boston, MA.

Khambaty, T., Stewart, J. C., Muldoon, M. F., & Kamarck, T. W. (2013, March). *Somatic-Vegetative Symptoms of Depression Predict 6-Year Increases in Insulin Resistance: Data from the Pittsburgh Healthy Heart Project*. Paper presented at the 71st Annual meeting of the American Psychosomatic Society, Miami, FL. (Young Scholar Award)

Vrany, E., Berntson, J., **Khambaty, T.**, & Stewart, J. C. (2013, March). *Somatic, but not Nonsomatic, Symptoms of Depression are Associated with Insulin Resistance: National Health and Nutrition Examination Survey (NHANES) 2005-2010.* Paper presented at the 71st Annual meeting of the American Psychosomatic Society, Miami, FL.

Khambaty, T., & Stewart, J. C. (2012, April). *Multiple Emotional Factors as Predictors of Cardiovascular Disease Incidence: Analysis of NHANES I Data.* Paper presented at the 33rd Annual meeting of the Society of Behavioral Medicine, New Orleans, LA. (Citation Abstract)

Poster Presentations at National Meetings:

Khambaty, T., Callahan C. M., & Stewart, J. C. (2015, March). *Depression Treatment and Diabetes Risk: A 9-Year Follow-up Study of the IMPACT Trial.* Poster presented at the 73nd Annual Scientific Meeting of the American Psychosomatic Society, Savannah, GA.

Khambaty, T., Stewart, J. C., Gupta, S. K., Chang, J., Butt, A., Gibert, C., Tindle, H., Crane, H., Bedimo R., & Freiberg, M. S. (2014, March). *Depressive Disorders Predict Incident Acute Myocardial Infarction in HIV+ Veterans: Veterans Aging Cohort Study*. Poster presented at the 2014 Annual Meeting of the Conference on Retroviruses and Opportunistic Infections, Boston, MA. (Young Investigator Award)

Stewart J. C., Gupta, S. K., **Khambaty, T.**, Berntson, J., Considine, R. V., & Callahan, C. M. (2014, March). *Effect of Computerized Depression Treatment on Endothelial Dysfunction: The Beating the Blues for Your Heart Pilot Trial.* Poster presented at the 72nd Annual Scientific Meeting of the American Psychosomatic Society, San Francisco, CA

Stewart, J. C., Hickman, R. J., & **Khambaty, T.** (2013, March). *C-Reactive Protein is Elevated in Atypical but not Nonatypical Depression: National Health and Nutrition Examination Survey (NHANES) 1999-2004*. Poster presented at the 71st Annual meeting of the American Psychosomatic Society, Miami, FL.

Berntson, J., Stewart, K. R., Vrany, E., **Khambaty, T.**, & Stewart, J. C. (2013, March). *Depressive Symptoms are Associated with Poor Adherence to Some Lifestyle but not Medication Recommendations to Prevent Cardiovascular Disease: National Health and Nutrition Examination Survey (NHANES) 2005-2010*. Poster presented at the 71st Annual meeting of the American Psychosomatic Society, Miami, FL.

Khambaty, T., & Stewart, J. C. (2012, April). *Multiple Emotional Factors and the Prevalence of Periodontal Disease: Analysis of NHANES I Data*. Poster presented at the 33rd Annual meeting of the Society of Behavioral Medicine, New Orleans, LA.

Khambaty, T., & Stewart, J. C. (2011, March). *Associations between Depressive and Anxiety disorders and Periodontal Disease: Analysis of 1999-2004 NHANES data*. Poster presented at the 69th Annual meeting of the American Psychosomatic Society, San Antonio, TX.

INVITED LECTURES AND COLLOQUIA

Khambaty, T. (2014, February). *Depressive Disorders Predict Incident Acute Myocardial Infarction in HIV+ Veterans: Veterans Aging Cohort Study.* One hour research conference presentation to the Indiana University School of Medicine Division of Infectious Diseases faculty and fellows, Indianapolis, IN.

Khambaty, T. (2013, March). *Clinical Case Presentation on Cognitive Behavioral Therapy for Depression: Sara.* A one hour clinical presentation at the IUPUI Department of Psychology Proseminar, attended by graduate students and faculty, Indianapolis, IN.

Khambaty, T. (2012, October). *Depression and Cardiovascular Disease (CVD): An Introduction.* Guest lecture to an Abnormal Psychology undergraduate class, Indianapolis, IN.

Khambaty, T. (2012, January). *The Role of Emotional Factors in Periodontal Disease.* A half-hour research presentation at the IUPUI Department of Psychology Proseminar, attended by graduate students and faculty, Indianapolis, IN.

RESEARCH ACTIVITIES

August 2014 -	**Healthy Outcomes for Patient Empowerment (HOPE)**
July 2015	Houston Center for Innovations in Quality, Effectiveness and Safety
	NCT01572389; November 2012-March 2016
	Principal Investigators: Aanand Naik, MD, Jeffrey Cully, PhD
	Veterans Health Administration, Health Services Research & Development
Roles:	Manuscript preparation; Protocol therapist
Study Objective:	Phase 3 multi-clinic, patient-level randomized controlled trial examining clinical effectiveness and preliminary implementation outcomes of a blended depression and diabetes behavioral health coaching intervention delivered by telephone

Duties:	Write and submit one first-author and one second-author manuscript based on baseline data; Deliver 9 telephone based intervention sessions over a six-month period; Sessions focus on physical and emotional health skills to address diabetes and depression based on principles of goal setting and action planning and evidence-based psychotherapy, including cognitive-behavioral therapy and motivational interviewing.
January 2011-March 2014	**Targeting Systemic Inflammation to Concurrently Treat Late Life Depression and Reduce Coronary Artery Disease Risk**
	R24 MH080827; January 2011-March 2014
	Principal Investigator: Jesse C. Stewart, PhD
	$465,718
	NIH/NIMH
Role:	Project coordinator; Protocol therapist
Study Objective:	Phase 2 randomized controlled trial evaluating whether pentoxifylline, a medication that interferes with the inflammatory cytokine cascade, is efficacious for concurrently treating late-life depression and endothelial dysfunction, an early marker of atherosclerotic cardiovascular disease.
Duties:	Trained and supervised research assistants; Implemented an internet treatment for depression among primary care patients in a medical setting; Screened for and appropriately addressed

	suicidality; Monitored and helped manage adverse events; Wrote and submitted IRB documents and amendments
January 2011 - June 2014	**Computer-Based Depression Treatment to Reduce Coronary Artery Disease Risk Pilot Clinical Trial**
	11CRP4880000; January 2011-July 2013
	Principal Investigator: Jesse C. Stewart, PhD
	$110,000
	American Heart Association
Role:	Project coordinator; Protocol therapist
Study Objective:	To evaluate whether an empirically supported, computer-based, cognitive behavioral intervention for depression - Beating the Blues® - delivered before the onset of cardiovascular disease, reduces coronary artery disease risk, indicated by brachial flow-mediated dilation, a noninvasive measure of endothelial function.
Duties:	Led project meetings with multi-disciplinary (doctors, nurses, ultrasonographers and the ResNet recruitment team) Indiana University and Wishard Hospital teams; Coordinated all study-related activities; Trained and supervised research assistants; Implemented an internet treatment for depression among primary care patients in a medical setting; Wrote and submitted IRB documents; Corresponded with IRB personnel to ensure ethical execution of scientific goals; Conducted data analyses and reviewed conference abstract.

January 2013 -	**Dissertation Research**
June 2014	Department of Psychology, IUPUI
Committee:	Christopher M. Callahan, MD
	Adam T. Hirsh, PhD
	Catherine E. Mosher, PhD
	Jesse C. Stewart, PhD
Summary:	Research indicates that depressive symptoms and disorders predict the onset and progression of type 2 diabetes. However, few clinical trials have evaluated the influence of pharmacological or psychological depression treatment on diabetes outcomes. Accordingly, I proposed a 9-year follow-up study of the Improving Mood-Promoting Access to Collaborative Treatment (IMPACT) trial to examine whether collaborative care for depression, including antidepressant medications and psychotherapy, reduces the likelihood of incident diabetes among otherwise healthy individuals (N=235). This is the first study to examine whether depression is a causal risk factor for incident type 2 diabetes. Findings were inconsistent with the notion that depression is a casual risk factor for diabetes and suggested that collaborative depression care alone is insufficient for reducing the excess diabetes risk of depressed, older adults.

January 2012 -	**Preliminary Examination Research**
December 2012	Department of Psychology, IUPUI
Committee:	Adam T. Hirsh, PhD
	Melissa A. Cyders, PhD, HSPP
	Jesse C. Stewart, PhD
Summary:	In this comprehensive literature review, I examined 78 studies that investigated the possible roles (i.e., Antecedent, Consequence, Epiphenomenon, or Moderator) that psychological distress, including negative emotional factors (e.g., depression, anxiety, and hostility/anger) or chronic stress (e.g., occupational, academic, marital, and financial stress), could have in the development, progression, and treatment of periodontal disease. This is the first review to (1) define these four potential roles, (2) critically evaluate both the direct empirical evidence and indirect evidence (i.e., plausibility) for or against these roles, and (3) develop a future research agenda for this area. In the review, I recommend that research in this area may benefit from collaborations between psychologists and dentists.
August 2009 -	**Master's Thesis Research**
December 2011	Department of Psychology, IUPUI
Committee:	Michelle P. Salyers, PhD
	Melissa A. Cyders, PhD, HSPP
	Jesse C. Stewart, PhD

Summary: Epidemiological studies suggest that depression may be an independent risk factor for cardiovascular disease (CVD). Although several possible mediators of this association have been proposed, the precise mechanisms are yet unknown. Accordingly, I examined periodontal disease as a novel mediator of the depression-CVD association, given its separate links with both depression and CVD. Data from the National Health and Nutrition Examination Survey (NHANES) I and its Epidemiologic Follow-up Study (NHEFS) were analyzed. Participants were 3,346 individuals aged 25-74 years free of CVD at baseline (53% female, 16% non-white). The primary outcome was incident CVD (N=727, 22%), defined as nonfatal or fatal coronary artery disease or cerebrovascular disease, identified during the follow-up period by interviews and death certificate records. Results suggested that (a) both periodontal disease and depressed mood are independent predictors of incident CVD and that (b) the effect of depressive symptoms on incident CVD is not mediated by periodontal disease.

June 2007 - May 2009 **Depression Research Laboratory**

Department of Psychology, Ohio State University, Columbus, OH

Role: Honors Thesis Student; Research Assistant

Duties: Administered the Structural Clinical Interview for Depression (SCID); Oriented participants to study protocol and Electronic

	Momentary Assessment devices; Collect heart rate variability data; Administered psychological assessments via Survey Monkey
December 2007 -	**Honors Thesis**
May 2009	Department of Psychology, Ohio State University, Columbus, OH
Committee:	Daniel R. Strunk, PhD
	Jennifer Cheavens, PhD
Summary:	Developed a research experiment to examine the association of diurnal mood variability with depressive symptoms, stress, and coping skills; Submitted IRB application for study approval; Developed research-related materials and questionnaires on Survey Monkey; Trained five undergraduate students in experimental procedures; Analyzed data using SAS software; Wrote and defended findings during a thesis committee meeting
September 2006 -	**Social Psychology Laboratory,**
May 2007	Department of Psychology, Ohio State University, Columbus, OH
Role:	Research Assistant
Duties:	Helped conduct various experiments in the lab; Administered computer based questionnaires and conducted experimental protocols and debriefing; Entered data for analyses
September 2005 -	**Behavioral Neuroscience Laboratory**
May 2006	Department of Psychology, Ohio State University, Columbus, OH
Role:	Research Assistant

Duties: Helped conduct T-maze experiments on spatial memory utilizing a rat model of Alzheimer's disease.

RESEARCH WORKSHOPS

August 2013	**Meta-Analysis**
	(Three day workshop)
Speaker:	Noel Card, PhD
	Associate Professor, University of Arizona
July 2013	**Scientific Writing from the Reader's Perspective with Dr. George Gopen**
	(Full day workshop)
Speaker:	George Gopen, PhD, JD
	Professor of the Practice of Rhetoric
	Senior Lecturing Fellow, Duke University
August 2012	**Structural Equation Modeling**
	(Three day workshop)
Speaker:	Gregory R. Hancock, PhD
	Professor and Chair, Measurement, Statistics and Evaluation
	Department of Human Development and Quantitative Methodology, University of Maryland

TEACHING ACTIVITIES

August 2010 -	**Undergraduate Capstone Course in Applied Psychology (B433)**
December 2010	Department of Psychology, IUPUI
Role:	Guest Lecturer
Duties:	Presented four lectures on utilizing SPSS software for statistical analyses of undergraduate class research projects.
August 2010 -	**Graduate Psychological Assessment Course (664)**
December 2010	Department of Psychology, IUPUI
Role:	Teaching Assistant
Duties:	Instructed first year graduate students in the administration of the WAIS-IV and WISC-IV; Graded integrated reports.
January 2010 -	**Undergraduate Capstone Course in Social Psychology (B471)**
May 2010	Department of Psychology, IUPUI
Role:	Teaching Assistant
Responsibilities*:*	Presented lectures; Evaluated student performance on class assignments and research projects.
August 2009 -	**Undergraduate Capstone Course in Applied Psychology (B433)**
December 2009	Department of Psychology, IUPUI
Position:	Teaching Assistant
Responsibilities:	Co-led three lectures on SPSS statistical analysis software; Evaluated student performance on class assignments.

SERVICE AND LEADERSHIP

March 2014 -	**Emerging Leader, Professional Education Committee**
Present	American Psychosomatic Society (APS)
Role:	Emerging leader
Duties:	Attend monthly conference calls with Professional Education Committee and alternate-monthly calls with other Emerging Leaders Initiative group; Review educational materials (e.g., conference presentations) for the APS website. Aid in the development of pre-conference workshops; Work with Emerging Leaders on outreach and promotion of the professional education mission of APS; Complete alternate-monthly progress reports
August 2012 -	**Search Committee for two tenure-track faculty members**
January 2013	Depart of Psychology, IUPUI, Indianapolis, IN
Role:	Student Representative
Duties:	Gathered and organized application materials via spreadsheets; Corresponded with applicants on an as needed basis; Created schedules for interview visits; Created brochures and advertisements for job-talks; Provided general help to applicants during their interview day.
August 2010 -	**Psychology Graduate Student Organization (PGSO)**
May 2011	Department of Psychology, IUPUI, Indianapolis, IN
Role:	Clinical Area Representative

Duties:	Gathered ideas for improvement from clinical area graduate students and relayed to organization board; Developed innovative methods to implement ideas.

PROFESSIONAL MEMBERSHIPS

2010 – Present	American Psychosomatic Society, Associate Member
2011 – Present	Indiana Psychological Society, Student Member
2012 – 2013	Society of Behavioral Medicine, Student Member

CLINICAL ACTIVITIES

January 2013 - May 2013	**Larue D. Carter Memorial Inpatient State Psychiatric Hospital** Indianapolis, IN
Role:	Practicum Student (290 hours)
Supervisors:	Kristine Chapleau, PhD, HSPP Timothy Lines, PhD, HSPP
Duties:	Conducted short- and long-term therapy using techniques from metacognitive therapy, dialectical behavioral therapy, and cognitive behavioral therapy with adults with severe mental illnesses (e.g., schizophrenia, and bipolar disorder); Led or co-led three therapy groups per week; Completed 7 psychosocial intake assessments at patient admission or annual review and offered diagnostic summaries; Individual therapy case-load of 4-6 patients

August 2012 -	**Inpatient Consultation-Liaison Psychiatry Service**
December 2012	Indiana University Hospital, Department of Psychiatry, Indianapolis, IN
Role:	Psychiatry Consultant (129 hours)
Supervisor:	David Fingerhut, PhD, HSPP
Duties:	Worked with an interdisciplinary team comprised of a psychiatrist, psychologist, and registered nurse; Conducted semi-structured interviews, and provided brief interventions with diverse patients (e.g., lower socioeconomic status clients on Medicare/Medicaid, self-pay clients, young and older adults) and presenting problems (depression, anxiety, panic disorder, psychosocial issues); Wrote concise evaluation notes in a timely manner; Communicated both within the Psychiatry team, members of other medical teams, and nursing staff to inquire about patient progress and report consultation findings; Attended rounds with the Neurology team to gain an interdisciplinary perspective.
January 2012 -	**Adult Outpatient Psychiatry Clinic**
July 2012	Indiana University School of Medicine Indianapolis, IN
Role:	Practicum Student (239 hours)
Supervisor:	Yelena Chernyak, PhD, HSPP
Duties:	Conducted initial intake assessments for patients; Provided individual therapy to patients presenting with a range of issues and

	psychiatric disorders (e.g., mood and anxiety disorders, bipolar disorder, insomnia, PTSD, academic difficulties and marital distress); Primary therapeutic modalities included cognitive-behavioral therapy and acceptance and commitment therapy; Developed evidence based treatment plans; Utilized established symptom inventories to monitor patient progress.
August 2011 - January 2012	**Community Bariatric Associates** Community South Hospital Indianapolis, IN
Role:	Practicum Student (259 hours)
Supervisor:	Theresa Rader, PsyD, HSPP
Duties:	Administered, scored, and interpreted an evidence-based assessment battery for patients seeking bariatric surgery; Assessed readiness for surgery and psychological functioning, including the presence of mood, anxiety, and personality disorders, coping skills, and brief cognitive functioning; Provided feedback and recommendations to patients orally and in written reports; Co-led 8-week bariatric educational groups focusing on diet, exercise, and cognitive-behavioral therapy and acceptance and commitment therapy techniques; Wrote 13 integrative reports.

January 2011 -	**St. Vincent Joshua Max Simon Primary Care Center**
July 2011	St. Vincent Family and Internal Medicine
	Indianapolis, IN
Role:	Student Behavioral Health Consultant (349 hours)
Supervisor:	Thomas Barbera, PhD, HSPP
Duties:	Work with an integrated care team of residents, attendings, nurses, psychiatrists, and social workers to provide brief individual therapy on issues of chronic pain, weight management, nicotine dependence, insomnia, drug and alcohol dependence, and mood/anxiety disorders; Primary therapeutic modality was cognitive-behavioral therapy; Conducted motivational interviewing for weight management and nicotine dependence; Provided relaxation training for anxiety; Utilized the electronic medical records system to review charts and write progress notes; Attended didactic seminars.
August 2010 -	**Post-Traumatic Stress Disorder Clinical Team (PCT)**
January 2011	Psychiatry Ambulatory Care Clinic (PACC)
	Richard L. Roudebush VA Medical Center
	Indianapolis, IN
Role:	Practicum Student (202 hours)
Supervisor:	David Tarr, PhD, HSPP
Duties:	Conducted individual therapy with male and female veterans presenting with PTSD, substance use disorders, mood/anxiety

disorders, and comorbid medical issues; Primary therapeutic modalities were cognitive-behavioral therapy and prolonged exposure; Developed recovery plans; Led or co-led cognitive-behavioral therapy group for depression, Sleep/Anger group, and peer support group; Attended staff meetings; Utilized CPRS electronic medical record system to write progress notes.

CLINICAL PEER SUPERVISION

January 2012 -	**Seminar in Teaching Psychology (I-595 graduate course)**
May 2012	Department of Psychology, IUPUI
Role:	Clinical Peer Supervisor to Rebecca N. Adams
Supervisor:	John Guare, PhD, HSPP
Duties:	Provided 1 hour of peer supervision two times per month to a second year Clinical Psychology PhD student during her first practicum placement.
August 2012 -	**Seminar in Teaching Psychology (I-595 graduate course)**
December 2012	Department of Psychology, IUPUI
Role:	Clinical Peer Supervisor to Kenny Karyadi
Supervisor:	John Guare, PhD, HSPP
Duties:	Provided 1 hour of peer supervision two times per month to a second year Clinical Psychology PhD student during his first practicum placement.

ASSESSMENTS ADMINISTERED

Diagnostic Assessments: Alcohol Use Disorder Test (AUDIT); Beck Anxiety Inventory (BAI); Beck Depression Inventory (BDI); Beck Depression Inventory-II (BDI-II); Blood Pressure Questionnaire; Brief Pain Inventory (BPI); Buss–Perry Aggression Questionnaire (BPAQ); Burn's EASY Diagnostic Survey; Drug Abuse Screening Test (DAST); Eating Attitudes Test (EAT-26); Generalized Anxiety Disorder 7-item scale (GAD-7); Geriatric Depression Scale (GDS); Headache Impact Test-6 item (HIT6); International Physical Activity Questionnaire (IPAQ);Mood Disorder Questionnaire (MDQ); Morisky Medication Adherence Questionnaire (MMAQ); Outcome Rating Scale; Patient Health Questionnaire-9 (PHQ-9); Positive and Negative Affect Schedule (PANAS); Pittsburgh Sleep Quality Index (PSQI); Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-I-CV); Symptom Checklist – 20 (SCL-20); Tobacco Use Questionnaire; Weight and Lifestyle Inventory (WALI); Zung Self-report Anxiety Scale

Intelligence and Achievement Assessments: Wechsler Adult Intelligence Scale (WAIS-IV); Wechsler Intelligence Scale for Children (WISC-IV); Wide Range Achievement Test – IV (WRAT-IV); Woodcock Johnson-III

Neuropsychological Assessments: Boston Naming Test (BNT); ; California Verbal Learning Test- Second edition (CVLT-II); Mini International Neuropsychiatric Interview (MINI) ; Mini-Mental Status Examination (MMSE); Paced Auditory Serial Addition Task (PASAT); Phonemic Fluency (FAS); PTSD CheckList (PCL); Repeatable Battery for the Assessment of Neuropsychological Status; Rey Auditory Verbal Learning Test; Satisfaction with Life Scale; Semantic Fluency (Animals); Stroop Color and Word Test

(STROOP); Trail Making Test (TMT); Test of Memory and Malingering (TOMM); Wisconsin Card Sorting Test (WCST); Word Memory Test (WMT)

Personality Assessments: Millon Behavioral Medicine Diagnostic (MBMD); Millon Clinical Multiaxial Inventory (MCMI); Minnesota Multiphasic Personality Inventory-Second Edition (MMPI-2); Minnesota Multiphasic personality Inventory-Second Edition Restructured Form (MMPI-2-RF); Rorschach Test; Thematic Apperception Test (TAT)

WORKSHOPS AND SPECIALTY TRAINING

October 2014	**The Many Faces of Diversity: Increasing Cultural Competence When Working With Veterans And Employees With Disabilities** (Full day workshop)
Speakers:	Linda R. Mona, PhD Clinical Psychologist, Director of Psychology Postdoctoral Training, Long Beach VA Medical Center Kevin Curtis, JD, LLM, VA Regional Council
September 2014	**Minnesota Multiphasic Personality Inventory-2-Restructured Form** (Full day workshop)
Speaker:	Paul A. Arbisi, PhD Department of Psychology, Minneapolis VA Medical Center, University of Minnesota
Spring 2014	**Biofeedback** (Half day workshop)
Speaker:	Eric L. Scott, PhD Assistant Professor of Clinical Psychology in Clinical Psychiatry Riley Hospital for Children

August 2010 -	**Metasupervision, Department of Psychology, IUPUI**
May 2013	(2-hour meeting monthly)
Supervisor:	John C. Guare, PhD, HSPP
Purpose:	Supervision meetings with students enrolled in practicum and a licensed practicum supervisor for the purpose of discussion progress in our respective practicum placements; Received supervision and feedback on audio recordings of therapy sessions
August 2009 -	**Proseminar in Clinical Psychology, Department of Psychology,**
May 2013	**IUPUI** (1-hour weekly departmental meeting)
Purpose:	Professional development course covering advanced clinical and research related topics via talks and presentations by invited speakers, and department faculty and students; Relevant topics included: diversity, internship and post-doctoral training and preparation, grant-writing, consulting, ethics, and supervision.
October 2013	**Consultation Seminar** (Half day workshop)
Speaker:	Susan Hickman, PhD
	Associate Professor, School of Nursing, IUPUI
August 2013	**Infusing Diversity into Teaching** (Half day workshop)
Speaker:	Leslie Ashburn-Nardo, PhD
	Associate Professor of Psychology, IUPUI

April 2013	**Self-Hypnosis Training for Chronic Pain Management**
	(Half day workshop)
Speaker:	Mark P. Jensen, PhD
	Associate Professor of Rehabilitation Science
	University of Washington
January 2013	**Consultation Liaison Supervision Training workshop**
	(Half day workshop)
Speaker:	Angie Rollins, PhD
	Research Scientist, Research Director
	Assertive Community Treatment (ACT) Center of Indiana
October 2011	**Clinical Supervision Training** (Full day workshop)
Speaker:	Julie Lash, PhD
	Director, Counseling and Psychological Services, UPUI
October 2011	**Consultation: The Compass Model** (Full day workshop)
Speaker:	Lisa Ruble, PhD
	Associate Professor, Educational, School, and Counseling
	Psychology, University of Kentucky
May 2011	**Group Schema Therapy for Borderline Personality Disorder**
	(Full day workshop)
Speaker:	Dr. Joan Farrell, PhD, and Ida Shaw, MSW
	Training Directors of the Center of BPD Treatment and Research,
	Department of Psychiatry
	Indiana University School of Medicine, Larue Carter Hospital

March 2010	**Evidence-based Practice: What Psychologists Need to Know and Why** (Full day workshop)
Speaker:	Barbara Walker, PhD Professor, Department of Psychological and Brain Sciences Indiana University, Bloomington