**Diabetes and depression: current understanding and future directions**

A report from the NIDDK International Conference on Diabetes and Depression

1Richard IG Holt FRCP

2Mary de Groot PhD

3Irwin Lucki PhD

4Christine M Hunter PhD

5Norman Sartorius FRCPsych

6Sherita H Golden MD

1Human Development and Health Academic Unit, Faculty of Medicine, University of Southampton, Southampton, UK

2Diabetes Translational Research Center, Indiana University School of Medicine, Indianapolis, IN, USA

3Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, USA

4National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, USA

5President, Association for the Improvement of Mental Health Programmes, Geneva, Switzerland, and Chairperson Dialogue on Diabetes and Depression

6Departments of Medicine and Epidemiology, Johns Hopkins University Schools of Medicine and Public Health, Baltimore, MD, USA

Address for Correspondence: Professor RIG Holt, The Institute of Developmental Sciences (IDS Building), MP887, University of Southampton, Southampton General Hospital, Tremona Road, Southampton SO16 6YD UK

Tel: +44 23 8079 4665, Fax: +44 23 8079 5255

Email address: [R.I.G.Holt@soton.ac.uk](mailto:R.I.G.Holt@soton.ac.uk)

Running title: Diabetes and depression

**Word Count:** main text: 4,340 Abstract: 236

Tables: 3 Figures: 1

**Abstract**

Diabetes and depression occur together approximately twice as frequently as would be predicted by chance alone. Co-morbid diabetes and depression are a major clinical challenge as the outcomes of both conditions are worsened by the other. This paper is based on discussions during an international meeting on diabetes and depression convened by the National Institute of Diabetes and Digestive and Kidney Diseases in collaboration with the National Institute of Mental Health and the Dialogue on Diabetes and Depression.

While the psychological burden of diabetes may contribute to depression in some cases, this explanation does not sufficiently explain the relationship between these two conditions. Shared biological and behavioral mechanisms, such as hypothalamic-pituitary-adrenal axis activation, inflammation, autonomic dysfunction, sleep disturbance, inactive lifestyle, poor dietary habits, and environmental and cultural risk factors, are important to consider in understanding the link between depression and diabetes.

Both individual psychological and pharmacological depression treatments are effective in people with diabetes but the current range of treatment options is limited and has shown mixed effects on glycemic outcomes. More research is needed to understand what factors contribute to individual differences in vulnerability, treatment response and resilience to depression and metabolic disorders across the life-course and how best to provide care for people with comorbid diabetes and depression in different healthcare settings. Training that will help to create a cross-disciplinary workforce that can work in different models of care for comorbid conditions is necessary.

**Introduction**

Epidemiological studies have shown that diabetes and depression occur together approximately twice as frequently as would be predicted by chance alone (1). Co-morbid diabetes and depression are a major clinical challenge as the outcomes of both conditions are worsened by the presence of the other (2). In October 2012, the National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH) in collaboration with the National Institute of Mental Health and the Dialogue on Diabetes and Depression (3), convened a meeting of experts from 15 countries to review the current evidence about the association between diabetes and depression and to identify gaps of knowledge that could be addressed by basic, clinical, behavioral, and public health research (4).

This paper is based on the presentations and discussions during that meeting and identifies areas where future research and training are needed. The conference presentations were divided into three main areas: (i) the mechanisms and pathogenesis underlying the depression-diabetes association, (ii) treatment of diabetes and depression and (iii) prevention and public health consideration of the two disorders.

* 1. **Methodological Considerations in Defining Depression**

Investigations of the psychosocial correlates and diabetes and depression treatment trials form the foundation of our existing knowledge base for the prevalence and impact of these co-morbid conditions. Although the core symptoms of depression are essentially the same across cultures, the presentation may vary because of patient’s and their immediate reference group’s perception of whether they are depressed; this perception will affect help-seeking behavior while the attribution of causation and issues such as stigma may differ between cultures (5).

Furthermore, the term “depression” covers a range of problems that span minor, occasional negative mood states to incapacitating and treatment-resistant disorders. The definition of “depression” varies markedly across studies ranging from high levels of self-reported depressive symptoms, diabetes-related distress to formal psychiatric diagnoses such as Major Depressive Disorder, Dysthymia or, Adjustment Disorder with Depressed Mood. Variability of measurement and use of terminology have contributed to inconsistency in the reported results of prevalence and treatment outcomes.

1. **Review of the Evidence**
   1. **Prevalence and Incidence of Diabetes and Depression**

The prevalence of co-morbid depressive symptoms and co-morbid depressive disorders are approximately 21-27% and 10-15% respectively in adults with type 1 and type 2 diabetes (1). There are few studies of the prevalence of depressive disorders in pediatric populations, but these suggest that the rates of depression, anxiety and distress are also elevated in children and young adults with type 1 diabetes compared to the general population with prevalence rates ranging from 10-26% (6). Similar rates are also seen in adolescents with type 2 diabetes or in populations with both type 1 and type 2 diabetes (8.6-14.8%) (7).

* 1. **Impact of co-morbid depression and diabetes**

In adults, there is only a weak relationship between depression and glycemic control (8). By contrast, there is a stronger association between co-morbid depressive symptoms and a range of diabetes complications (9), although this was not observed in the recent Action to Control CardiovascularRisk in Diabetes Trial (10). Increased healthcare costs (11), worsened functional disability (12) and early mortality are seen in adults with co-morbid diabetes and depression compared to either condition alone (13). Higher mortality among those with diabetes and depression is attributable to a variety of medical causes rather than primarily cardiovascular disease as previously assumed (13;14) and is not wholly explained by traditional risk factors (15). In children and adolescents, depressive symptoms are associated with poorer glycemic control (6) and predict re-hospitalization and retinopathy in children with type 1 diabetes (16;17).

* 1. **The Mechanisms and Pathogenesis Underlying the Association between Diabetes and Depression**

Figure 1 summarizes common pathogenic mechanisms and their interrelations discussed during the conference, although it is acknowledged that other postulated pathogenic mechanisms linking these two disorders may exist. Both basic science and clinical research studies suggest that a predisposition to depression and diabetes are influenced by environmental factors which in turn may affect several biological pathways, including the hypothalamic-pituitary adrenal (HPA) axis, the inflammatory cytokine pathway, and circadian rhythms, likely through adaptive epigenetic changes, that influence the risk for developing mental health (i.e. depression) and metabolic disorders (i.e. diabetes). The relative importance of these risk factors in provoking depression in people with diabetes is currently unknown.

Previous epidemiological studies have demonstrated a bi-directional association between depression and diabetes (18;19) and most prior work has focused on understanding potential mechanisms by which diabetes leads to depression and vice versa. The shared biological mechanisms, however, suggest a novel perspective in considering the link between depression and diabetes. Focusing more on mechanisms common to the development of both depression *and* diabetes rather than focusing on the direction of association may yield novel insights for developing improved approaches to prevention and treatment. In turn, this may lead to treatment and preventative strategies to address these two major public health burdens simultaneously.

The traditional view of co-morbid diabetes and depression assumed that the self-care burden of diabetes, coupled with the knowledge of the diagnosis of diabetes and complications, rendered the patient with feelings of helplessness and hopelessness that resulted in depression. While there is evidence to support this model (20), it does not account for a number of biological changes in diabetes, such as structural, functional and neurochemical changes in the brain regions responsible for affect and cognition in both type 1 and type 2 diabetes, that may increase the risk of depression (21). Similarly the increased rate of diabetes in people with depression has been attributed to obesity-promoting health behaviors, such as physical inactivity and poor dietary habits (19) but this ignores the biological changes of depression.

* + 1. Intrauterine environment

The earliest influence is the intrauterine environment and early life conditions, such as prenatal undernutrition and stress and maternal stress, which can lead to low birth weight and a predisposition to adult diabetes (22). Animal studies have shown an adaptive slowing of fetal growth rate and modification of organ structure in response to undernutrition (23). The data about the relationship between adverse intrauterine environment and risk for depression in adulthood remain inconclusive, with some studies suggesting a positive association while others having null findings (24). In human studies, both low birth weight and fetal overexposure to cortisol secondary to maternal stress have been associated with HPA axis programming and elevated cortisol reactivity in childhood, adolescence and adulthood, predisposing the individual to stress-related and metabolic disorders (25).

* + 1. External environment

Several contextual factors, including childhood adversity, possibly mediated through increased adult C-reactive protein concentration (26), neighborhood environment, and poverty also influence the predisposition to depression and diabetes.

Poorer neighborhood physical environment (e.g. physical disorder, traffic, noise, decreased walkability) is associated with worse diet and lower physical activity patterns, obesity, diabetes, hypertension and depression (27). Furthermore, worse neighborhood social environment (e.g. lower social cohesion and social capital, increased violence, decrease residential stability) is associated with higher rates of depression and mental health problems (28). Cross-sectional datasets have indicated that resources promoting physical activity and healthy diets are associated with lower diabetes risk (29). Adverse neighborhood environments have also been associated with dysfunctional HPA axis activity and disruption of its normal circadian rhythm (i.e. blunted profile) (30-34) as well as enhanced inflammation (35;36).

* + 1. Common interrelated biological pathways

Both depression and diabetes are associated with HPA axis dysfunction, which manifests as subclinical hypercortisolism, blunted diurnal cortisol rhythm, or hypocortisolism with impaired glucocorticoid sensitivity, and increased inflammation (37-40). Disrupted sleep patterns are associated with depression (41) while poor sleep quality and altered circadian rhythms are associated with insulin resistance and type 2 diabetes risk (42). All these biological pathways are activated in depression and are associated with insulin resistance. A recent meta-analysis showed that depressive symptoms are weakly associated with insulin resistance, providing a potential link to incident type 2 diabetes (43).

* + 1. Pathways related to medications for depression

While there have been concerns that certain antipsychotic medications, particularly some of the “atypical” or second generation antipsychotic medications, are associated with a 2-3 fold increased risk of diabetes (44), recently a role of antidepressants in the development of diabetes has been postulated (45). Cohort studies show a small increased risk of diabetes in those receiving antidepressant medications. Randomized controlled trials, however, have emphasized that antidepressants vary considerably in their propensity for weight gain (46) and glycemic effects ranging from hyperglycemic to hypoglycemic effects (45). It remains unclear whether the weight gain results from poorly treated depression or a medication side effect. The precise mechanisms by which these drugs may lead to weight gain and altered intermediate metabolism are unknown, not least because they may affect multiple neurotransmitter receptors simultaneously (45;46).

* 1. **Treatment of Diabetes and Depression**

Until recently, people with diabetes were specifically excluded from depression treatment trials in the general population and consequently, there are relatively few studies examining antidepressant and psychotherapy treatment of depression that specifically focus on diabetes.

* + 1. Psychotherapy

Psychotherapy treatment protocols for depression in people with diabetes have predominantly used cognitive behavioral therapy (CBT) delivered individually by mental health providers or trained nurse case managers and are effective in reducing depressive symptoms in adults. Although there are mixed effects on glycemic control, interventions that combine diabetes self-management education reported benefits for glycemic control (47).

Although a small research base exists, more research is needed to test alternative behavioral intervention approaches for treating diabetes and depression (e.g. e-Health, exercise, mindfulness-based stress reduction), not least because trials of e-health and m-health interventions suggest that these are less effective than face-to-face psychotherapeutic treatments (48).

There is a lack of evidence for psychotherapy in children. Given the nature of pediatric diabetes management, it is questionable whether individually based psychological therapy is the best choice, because this ignores the “family nature” of diabetes care for children.

* + 1. Antidepressants

Antidepressant medications lead to amelioration of depression in people with either type 1 or type 2 diabetes but with mixed effects on glycemic control ranging from hyperglycemic effects with tricyclic antidepressant medications to euglycemic or slightly hypoglycemic effects with selective serotonin reuptake inhibitors (SSRI) and serotonin–noradrenaline reuptake inhibitors (SNRI) (47). Fewer than half of the commonly prescribed SSRI and SNRI medications have been tested for their effects on glycemic control in people with diabetes. Trials have not been designed to assess differences in the effectiveness of these medications by diabetes type.

* + 1. Collaborative Care

Multidisciplinary team approaches to the identification and treatment of depression within primary care settings incorporate identification of high risk cases, problem-solving therapy delivered by trained nurse case managers, and medications using a stepped-care approach (49). The PATHWAYS study indicated positive improvements in depression outcomes among adults with type 1 and type 2 diabetes but no changes in glycemic control (49). The subsequent TEAMCare approach combined behavioral and pharmacological treatment of depression with diabetes management leading to positive outcomes for depression and glycemic, systolic blood pressure and LDL cholesterol control and reduced health care costs (50).

**Prevention and Public Health Considerations**

The high prevalence of co-morbid diabetes and depression has a number of public health ramifications particularly at the present time when many healthcare systems are becoming increasingly fragmented and specialized. This disadvantages individuals with co-morbid physical and mental illness. The UK Disability Rights Commission has highlighted the concept of “overshadowing” where healthcare professionals focus solely on the mental disorder and fail to take note of physical health needs, despite the greater need for this care (51). This translates into poorer diabetes care as those with mental illness are less likely to be screened for diabetes leading to higher rates of undiagnosed diabetes (52). People with co-morbid mental illness are less likely to be offered screening for glycated hemoglobin or cholesterol, statin therapy, or diabetes education, or be examined for microvascular complications, despite more clinic visits. By contrast, depressive and other mental disorders are often missed and inadequately treated if the focus of care is the medical condition (53;54). These types of systematic deficiencies within healthcare systems may contribute significantly to the poorer health outcomes in those with co-morbid diabetes and depression.

A recent systematic review has highlighted the increased health service utilization and cost associated with co-morbid diabetes and depression (11). In addition to direct health costs, adverse impacts on workforce participation and absenteeism were also found. A limitation of these studies is that most were undertaken in the U.S., with few examining the impact beyond one year or outside the health care system.

* + 1. Prevention of diabetes in people with depression

Recent studies have shown that diabetes can be prevented, or at least delayed, by either lifestyle or pharmacological interventions (55). The development of diabetes risk engines now allows a reasonably accurate assessment of diabetes risk in clinical practice. This combination of better identification and affordable interventions has made diabetes prevention a realistic and cost-effective proposition (56).

Neither the risk engines nor diabetes prevention interventions have been evaluated in people with depression. This is important because the risk of diabetes is increased in people with depression and may involve different etiologic factors while a number of barriers may impede the successful implementation of lifestyle interventions. In the Diabetes Prevention Program, those taking antidepressants had a higher risk of developing diabetes than those not taking antidepressants in the placebo and lifestyle intervention arms, while in the metformin arm, the risk was lower (57;58). This study excluded those with severe depression and the wide confidence intervals of the findings make it unclear whether these findings can be extrapolated to a broader population of people with depression. Nevertheless it should not be assumed that risk identification and prevention will be equally effective in people with depression in the absence of scientific evidence.

* + 1. Prevention of depression in people with diabetes

Many risk factors that predict the onset of depression in the general population are equally applicable to people with diabetes but there are several diabetes specific factors, such as the development of complications (9) and the need for insulin treatment in people with type 2 diabetes (59), which are associated with an increased prevalence of depression. Despite our understanding of the epidemiology, there has been little research into the prevention of depression in people with diabetes. This is also true in people without diabetes, where most interventions have focused on secondary prevention. A recent systematic review concluded that there was inadequate evidence to determine the clinical effectiveness or cost-effectiveness of low-intensity psychological interventions to prevent relapse or recurrence of depression (60).

The large numbers of people with diabetes at risk of depression demand efficacious and cost-effective interventions. This may involve the use of non-professional workers, for example peers, or new technologies to deliver the preventative interventions.

* + 1. Primary prevention of depression and diabetes

There are many shared risk factors for diabetes and depression suggesting that diabetes and depression may be two manifestations of a common set of psychological, lifestyle and biological perturbations. It is therefore possible that population approaches that focus on the common ground between diabetes and depression and the behaviors that relate to both may allow the effective prevention of both conditions but this area is largely unresearched.

1. **Research Recommendations**

There are critical gaps and key opportunities to improve our understanding of the prevalence, impact, mechanism, treatment and public health considerations of the depression-diabetes association. This section highlights the key recommendations made during the meeting. Greater detail of the recommendations can be found in tables 1-3.

* 1. **Phenomenology**

Much greater clarity and specificity is needed to describe and measure depressive symptoms and their various combinations not amounting to specific disorders in the depressive spectrum. Prospective longitudinal studies of depression spectrum (e.g. major depressive disorder, dysthymia, etc.) and other psychiatric diagnoses, such as bipolar disorders or psychotic disorders, are needed in separate populations of people with type 1 and type 2 diabetes to characterize inception predictors as well as the course of comorbidity. There is a particular need for studies in children and adolescents with diabetes where there is a paucity of knowledge. More detailed description and study of diabetes subtypes, including gestational diabetes and impaired glucose metabolism, and phenotypes (age, ethnicity, body mass index, diabetes duration, comorbidities, treatment etc.) are needed to clarify the onset and co-morbidity of depression and diabetes.

* 1. **Mechanisms**

Research to understand the depression-diabetes association and uncover potential mechanisms of that relationship will require various designs and approaches. Observational studies across the life course may shed light on mechanisms linking depression and diabetes including identifying novel biomarkers to assess risk or evaluate the effectiveness of interventions. Secondary analysis of existing cohort studies with longitudinal data on depression, diabetes, and banked serum should be optimized. Prospective data collection in cohorts with diverse sociocultural characteristics is also needed to understand the occurrence and progression of both disorders. Data are needed to understand the cumulative effect of multiple environmental stimuli, how they interact with intrinsic biological changes and how they influence vulnerability or resilience to mental health and metabolic disorders to identify potential intervention periods and targets.

Experimental studies should be designed to identify biomarkers that translate animal models of depression and diabetes to humans. Interventional studies in animal models and humans should examine the impact of experimental therapies on proposed biological and behavioral pathways common to depression and diabetes. An understanding of the biological mechanisms linking depression and diabetes through identification of biomarkers, specimens, and PET scanning may allow development of interventions aimed at the implicated physiological pathways. Finally, more research is needed in animal models and human studies to identify the non-CVD mediators of early mortality associated with diabetes and depression.

Future studies should focus on enhancing our understanding of individual differences in vulnerability and resilience to depression and metabolic disorders following exposure to adverse intrauterine and extra-uterine environments. These studies require a life course approach that facilitates examination of the cumulative effect of multiple environmental stimuli and explore how they interact with intrinsic biological changes and affect vulnerability to mental health and metabolic disorders. Longitudinal study designs are needed to measure the associations among depression, diabetes, the environment, and the role of positive emotional health behavior and glycemic outcomes.

An understanding of the biological mechanisms linking depression and diabetes through use of biomarkers, specimens, and PET scanning may allow development of interventions aimed at the implicated physiological pathways. Finally, more research is needed in animal models and human studies to identify the non-CVD mediators of early mortality associated with diabetes and depression.

* 1. **Treatment of Diabetes and Depression**
     1. Depression Screening

Depression screening is an important first step for the identification of individuals that could benefit from treatment. The use of locally standardized screening instruments, such as PHQ-9, that may be widely used in primary care and provide consistent definitions of what constitutes depressive symptom thresholds or cases of ‘depression’ would facilitate comparative studies of depressive disorders in different cultures within and across countries. However, this approach must be evaluated in concert with intervention trials to assess clinical and cost effectiveness (61).In the context of U.S. health care reform, there is an opportunity to develop routine surveillance using electronic medical records for the risk of depression and alert providers to intervene proactively. Such surveillance of the quality and patterns of diabetes care would allow large scale evaluation of natural experiments that occur in health care delivery systems (62).

* + 1. Treatment Modalities and Delivery

Despite well-understood differences in the etiology and pathophysiology of type 1 and type 2 diabetes, existing treatment studies have examined mixed populations making generalizations about treatment efficacy of antidepressant medications or psychotherapy by diabetes type difficult (47). Sample sizes for sub-groups of people with type 1 diabetes within existing studies are too small to allow stratified analyses to determine similarities or differences in treatment modalities and outcomes compared with adults with type 2 diabetes. Studies that highlight whether differences occur between diabetes type are needed.

Within the psychotherapy literature, the use of multiple simultaneous strategies common to CBT makes it unclear which strategies contribute to improved outcomes. Research should clarify this along with ‘dose effects’ of CBT in patients to determine which psychotherapeutic strategies (cognitive restructuring, problem solving, activation, interpersonal therapy, etc.) are most effective for which patients (e.g. type 1, type 2, gestational) under different treatment conditions (e.g. severity of diabetes and co-morbid conditions).

There is a need to expand treatment modalities beyond CBT to include additional approaches such as exercise and/or community based programs that link treatment to community resources beyond health care systems such as in-home (63) or community-based treatment programs (64). Empirically validated treatment approaches that make use of support systems (e.g. ecological approach) are needed to treat both depressive disorders as well as diabetes-related distress making use of all possible mental health partners and allied health advocates (e.g. fitness instructors, community health workers) in a multidisciplinary approach.

There is a need to evaluate mechanisms of pharmacological treatment using adequately powered clinical trials. Greater understanding about the way psychotropic medications interact with other risk factors and the effects of antidepressants on diabetes prevention, metabolic risk, and patient safety in discrete samples of people with different types of diabetes is needed. Such studies should permit comparisons of the impact of the factors listed above in people belonging to different sociocultural groups.

* 1. **Prevention and Public Health Considerations** 
     1. Prevention

It is unclear whether effective prevention or treatment of depression can reduce incidence of type 2 diabetes. Future trials are needed to address this issue while validation of diabetes risk engines in people with depression is needed to identify those at high risk of diabetes. The interaction of depression and antidepressants on interventions to prevent diabetes also merits further study.

Future research should examine when and how interventions to prevent depression can be introduced in people with diabetes. Such research should be conducted in people with diabetes in both primary and specialty care settings to evaluate the effectiveness of interventions using established methods and functional outcomes. The timing of these interventions in relation to the diagnosis of diabetes should be considered. Given the burden of diagnosis, interventions aimed at healthcare professionals providing care at the time of diabetes diagnosis should be considered. Research into the facilitators of and barriers to healthcare professionals’ engagement with co-morbidity is needed. Health services research is required to find the optimal way of delivering interventions.

Currently researched models of care often do not match the reality of the primary care and so alternative methodologies such as Practice Based Research Networks, pragmatic trials, systems science, and longer-term observational studies that include patient reported outcomes should be considered.

Population based interventions to reduce common etiological factors for diabetes and depression should be developed and tested in experimental studies.

* + 1. Public Health Considerations

Translating basic and clinical research findings into improved treatment and outcomes remains a substantial challenge. While multidisciplinary team care approaches have shown efficacy for both diabetes and depression, much work remains to identify the methodologies and infrastructure needed to deliver and implement best practice into routine health care in an economically sustainable manner. Given the cross-specialty nature of co-morbid diabetes and depression, further research is needed to identify how healthcare professional working across different disciplines can provide integrated health services for people with co-morbidity. Additional work to develop technologies to extend collaborative care (e.g. telemedicine, patient registries, e-Health, m-Health) to patients and providers is needed while weighing the relative benefits of depression control in light of multiple health outcomes (e.g. glucose, blood pressure, lipid and tobacco control). National and local initiatives to develop payment approaches to support case management are needed to insure the successful implementation of large scale integrated care interventions.

Most of the published economic analyses of the co-morbidity of diabetes and depression have been undertaken in the U.S.; further research is needed in other parts of the world. Collaborative studies using cross-culturally applicable assessment methods would be valuable because they would clarify the impact of culture on the presentation, course and outcome of depression and diabetes and allow the development of different yet effective interventions and models of service. Longer term studies that take a broader view of the costs, including non-healthcare related costs, are needed to evaluate cost effectiveness since cost benefits are not usually realized immediately.

* 1. **Training for Research and Clinical Care**

Training is needed to enhance the workforce involved in both research and clinical care of diabetes and depression. Many researchers and practitioners currently work within single disease fields. It is critical that training moves study and practice to account for the complexity of multiple co-morbid diseases that are the norm for real world patients. Training should promote the development of cross-disciplinary researchers who can work in teams to understand the mechanisms of co-morbid conditions better and develop effective prevention and treatment approaches. Researchers with basic science and clinical research expertise in neuroscience, neuroendocrinology, neuroimmunology, behavioral science, clinical psychology, public health, clinical trials, and medicine (e.g., psychiatry, internal medicine, pediatrics) will all be necessary to advance this field. As well as working across disciplines, training is needed to develop researchers who can move across different levels of the translational continuum from basic to applied clinical, behavioral and population science and back again. As in many fields, scientific advancement is stunted without a cadre of researchers that can span the translational chasms between the basic, applied, and population sciences.

Training to expand the workforce healthcare professionals and extenders (e.g. community health workers, peer supporters) adept in managing co-morbid depression and diabetes is needed. However, given the scope of the needs in high-, middle- and low income countries, cost efficient approaches to expanding the workforce will be critical. Mental health providers, diabetes behavioral researchers, diabetologists, diabetes educators, primary care providers, nursing and mid-level provider staff and community based providers are some examples of professions where additional training in detection, prevention and treatment related to co-morbid diabetes and depression could be beneficial.

1. **Conclusion**

The association between diabetes and depression is a major public health problem. To resolve it and to improve the outcomes for people with co-morbid diabetes and depression, a more detailed understanding of the association is needed together with the introduction of evidence-based interventions into health care.

**Disclaimer**

The opinions expressed herein and the interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official recommendation, interpretation, or policy of the National Institutes of Health or the U.S. Government or of the Dialogue on Diabetes and Depression or of the Association for the Improvement of Mental Health Programmes,.

**Acknowledgements**

We acknowledge the support of the US National Institutes of Health (NIDDK and NIMH) and of the Dialogue on Diabetes and Depression which was established in 2008 as an international collaboration with the aim of addressing the challenges of co-morbid diabetes and depression (3). The goals of the Dialogue on Diabetes and Depression include the coordination of research, the development of training materials, the organization of symposia and training courses, the production of reviews of knowledge as well as the facilitation of collaboration among countries, organizations and clinical and scientific experts to prevent or reduce the sequelae of these co-morbid conditions.

We would like to acknowledge the following who contributed to the meeting:

Planning Committee: Mary de Groot, Sherita Golden, Richard Holt, Christine Hunter, Wayne Katon, Irwin Lucki, Paul Muehrer, Norman Sartorius, Larry Cimino

Speakers and Moderators: Orefeu Buxton, Santosh Chaturvedi, Paul Ciechanowski, Robert Dantzer, Mary de Groot, Leonard Egede, David Ehrmann, Edwin Fisher, Tiffany Gary-Webb, Sherita Golden, Jeff Gonzalez, John Hayes, Richard Holt, Khalida Ismail, Alan Jacobson, Wayne Katon, Maria Kovacs, Irwin Lucki, David Marrero, David McDaid, Arie Nouwen, Patrick O’Connor, Brian Oldenberg, Francois Pouwer, Charles Raison, Robert Ratner, Richard Roberts, Norman Sartorius, Alexis Stranahan, Christina van der Feltz-Cornelis, Rachel Whitmer

We would also like to acknowledge the following who provided helpful comments during the preparation of this paper: Robert Dantzer, Edwin Fisher, Alan Jacobson, Wayne Katon, Maria Kovacs, Robert Ratner

**Conflict of Interest**

RIGH has acted as an advisory board member and speaker for Novo Nordisk, and as a speaker for Sanofi-Aventis, Eli Lilly, Otsuka and Bristol-Myers Squibb. He has received grants in support of investigator trials from Novo Nordisk. NS has received grants or research support from Pfizer, Lilly and honoraria or consultation fees from Lundbeck, Servier, Eli Lilly, Takeda and Roche.

**Author Contributions**

All authors were members of the organizing committee of the NIDDK International Conference on Diabetes and Depression and presented at the conference. RIGH wrote the first draft with support from MdeG and SG. All authors then critically reviewed and edited the paper. RIGH is the guarantor for the paper.

Reference List

(1) Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. Diabetes Care 2001 Jun;24(6):1069-78.

(2) Holt RI, Katon WJ. Dialogue on Diabetes and Depression: Dealing with the double burden of co-morbidity. J Affect Disord 2012 Oct;142 Suppl:S1-S3.

(3) Sartorius N, Cimino L. The Dialogue on Diabetes and Depression (DDD): Origins and achievements. J Affect Disord 2012 Oct;142 Suppl:S4-S7.

(4) International Conference on Diabetes and Depression. http://www2.niddk.nih.gov/News/Calendar/DiabetesDepression12.htm Last accessed 07/09/2013

(5) Fisher EB, Chan JC, Nan H, Sartorius N, Oldenburg B. Co-occurrence of diabetes and depression: conceptual considerations for an emerging global health challenge. J Affect Disord 2012 Oct;142 Suppl:S56-S66.

(6) Reynolds KA, Helgeson VS. Children with diabetes compared to peers: depressed? Distressed? A meta-analytic review. Ann Behav Med 2011 Aug;42(1):29-41.

(7) Anderson BJ, Edelstein S, Abramson NW, Katz LE, Yasuda PM, Lavietes SJ, et al. Depressive symptoms and quality of life in adolescents with type 2 diabetes: baseline data from the TODAY study. Diabetes Care 2011 Oct;34(10):2205-7.

(8) Lustman PJ, Anderson RJ, Freedland KE, de GM, Carney RM, Clouse RE. Depression and poor glycemic control: a meta-analytic review of the literature. Diabetes Care 2000 Jul;23(7):934-42.

(9) de Groot M, Anderson R, Freedland KE, Clouse RE, Lustman PJ. Association of depression and diabetes complications: a meta-analysis. Psychosom Med 2001 Jul;63(4):619-30.

(10) Sullivan MD, O'Connor P, Feeney P, Hire D, Simmons DL, Raisch DW, et al. Depression predicts all-cause mortality: epidemiological evaluation from the ACCORD HRQL substudy. Diabetes Care 2012 Aug;35(8):1708-15.

(11) Molosankwe I, Patel A, Jose GJ, Knapp M, McDaid D. Economic aspects of the association between diabetes and depression: a systematic review. J Affect Disord 2012 Oct;142 Suppl:S42-S55.

(12) Egede LE. Diabetes, major depression, and functional disability among U.S. adults. Diabetes Care 2004 Feb;27(2):421-8.

(13) Park M, Katon WJ, Wolf FM. Depression and risk of mortality in individuals with diabetes: a meta-analysis and systematic review. Gen Hosp Psychiatry 2013 May;35(3):217-25.

(14) Lin EH, Heckbert SR, Rutter CM, Katon WJ, Ciechanowski P, Ludman EJ, et al. Depression and increased mortality in diabetes: unexpected causes of death. Ann Fam Med 2009 Sep;7(5):414-21.

(15) O'Connor PJ, Narayan KM, Anderson R, Feeney P, Fine L, Ali MK, et al. Effect of intensive versus standard blood pressure control on depression and health-related quality of life in type 2 diabetes: the ACCORD trial. Diabetes Care 2012 Jul;35(7):1479-81.

(16) Stewart SM, Rao U, Emslie GJ, Klein D, White PC. Depressive symptoms predict hospitalization for adolescents with type 1 diabetes mellitus. Pediatrics 2005 May;115(5):1315-9.

(17) Kovacs M, Mukerji P, Drash A, Iyengar S. Biomedical and psychiatric risk factors for retinopathy among children with IDDM. Diabetes Care 1995 Dec;18(12):1592-9.

(18) Mezuk B, Eaton WW, Albrecht S, Golden SH. Depression and type 2 diabetes over the lifespan: a meta-analysis. Diabetes Care 2008 Dec;31(12):2383-90.

(19) Golden SH, Lazo M, Carnethon M, Bertoni AG, Schreiner PJ, Diez Roux AV, et al. Examining a bidirectional association between depressive symptoms and diabetes. JAMA 2008 Jun 18;299(23):2751-9.

(20) Nouwen A, Nefs G, Caramlau I, Connock M, Winkley K, Lloyd CE, et al. 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 2011 Mar;34(3):752-62.

(21) Lyoo IK, Yoon S, Jacobson AM, Hwang J, Musen G, Kim JE, et al. Prefrontal cortical deficits in type 1 diabetes mellitus: brain correlates of comorbid depression. Arch Gen Psychiatry 2012 Dec;69(12):1267-76.

(22) Berends LM, Ozanne SE. Early determinants of type-2 diabetes. Best Pract Res Clin Endocrinol Metab 2012 Oct;26(5):569-80.

(23) Kuzawa CW, Sweet E. Epigenetics and the embodiment of race: developmental origins of US racial disparities in cardiovascular health. Am J Hum Biol 2009 Jan;21(1):2-15.

(24) Kajantie E, Raikkonen K. Early life predictors of the physiological stress response later in life. Neurosci Biobehav Rev 2010 Sep;35(1):23-32.

(25) Phillips DI. Programming of the stress response: a fundamental mechanism underlying the long-term effects of the fetal environment? J Intern Med 2007 May;261(5):453-60.

(26) Slopen N, Koenen KC, Kubzansky LD. Childhood adversity and immune and inflammatory biomarkers associated with cardiovascular risk in youth: a systematic review. Brain Behav Immun 2012 Feb;26(2):239-50.

(27) de Vet E, de Ridder DT, de Wit JB. Environmental correlates of physical activity and dietary behaviours among young people: a systematic review of reviews. Obes Rev 2011 May;12(5):e130-e142.

(28) Mair C, Diez Roux AV, Galea S. Are neighbourhood characteristics associated with depressive symptoms? A review of evidence. J Epidemiol Community Health 2008 Nov;62(11):940-6, 8.

(29) Auchincloss AH, Diez Roux AV, Brown DG, Erdmann CA, Bertoni AG. Neighborhood resources for physical activity and healthy foods and their association with insulin resistance. Epidemiology 2008 Jan;19(1):146-57.

(30) Skinner ML, Shirtcliff EA, Haggerty KP, Coe CL, Catalano RF. Allostasis model facilitates understanding race differences in the diurnal cortisol rhythm. Dev Psychopathol 2011 Nov;23(4):1167-86.

(31) Brenner AB, Zimmerman MA, Bauermeister JA, Caldwell CH. The physiological expression of living in disadvantaged neighborhoods for youth. J Youth Adolesc 2013 Jun;42(6):792-806.

(32) Karb RA, Elliott MR, Dowd JB, Morenoff JD. Neighborhood-level stressors, social support, and diurnal patterns of cortisol: the Chicago Community Adult Health Study. Soc Sci Med 2012 Sep;75(6):1038-47.

(33) Do DP, Diez Roux AV, Hajat A, Auchincloss AH, Merkin SS, Ranjit N, et al. Circadian rhythm of cortisol and neighborhood characteristics in a population-based sample: the Multi-Ethnic Study of Atherosclerosis. Health Place 2011 Mar;17(2):625-32.

(34) Dulin-Keita A, Casazza K, Fernandez JR, Goran MI, Gower B. Do neighbourhoods matter? Neighbourhood disorder and long-term trends in serum cortisol levels. J Epidemiol Community Health 2012 Jan;66(1):24-9.

(35) Browning CR, Cagney KA, Iveniuk J. Neighborhood stressors and cardiovascular health: crime and C-reactive protein in Dallas, USA. Soc Sci Med 2012 Oct;75(7):1271-9.

(36) Broyles ST, Staiano AE, Drazba KT, Gupta AK, Sothern M, Katzmarzyk PT. Elevated C-reactive protein in children from risky neighborhoods: evidence for a stress pathway linking neighborhoods and inflammation in children. PLoS One 2012;7(9):e45419.

(37) Champaneri S, Wand GS, Malhotra SS, Casagrande SS, Golden SH. Biological basis of depression in adults with diabetes. Curr Diab Rep 2010 Dec;10(6):396-405.

(38) Stetler C, Miller GE. Blunted cortisol response to awakening in mild to moderate depression: regulatory influences of sleep patterns and social contacts. J Abnorm Psychol 2005 Nov;114(4):697-705.

(39) Champaneri S, Xu X, Carnethon MR, Bertoni AG, Seeman T, Diez RA, et al. Diurnal salivary cortisol and urinary catecholamines are associated with diabetes mellitus: the Multi-Ethnic Study of Atherosclerosis. Metabolism 2012 Jul;61(7):986-95.

(40) Stetler C, Miller GE. Depression and hypothalamic-pituitary-adrenal activation: a quantitative summary of four decades of research. Psychosom Med 2011 Feb;73(2):114-26.

(41) Courtet P, Olie E. Circadian dimension and severity of depression. Eur Neuropsychopharmacol 2012;22 Suppl 3:S476-S481.

(42) Gangwisch JE. Epidemiological evidence for the links between sleep, circadian rhythms and metabolism. Obes Rev 2009 Nov;10 Suppl 2:37-45.

(43) Kan C, Silva N, Golden SH, Rajala U, Timonen M, Stahl D, et al. A systematic review and meta-analysis of the association between depression and insulin resistance. Diabetes Care 2013 Feb;36(2):480-9.

(44) Holt RI, Peveler RC. Antipsychotic drugs and diabetes--an application of the Austin Bradford Hill criteria. Diabetologia 2006 Jul;49(7):1467-76.

(45) Barnard K, Peveler RC, Holt RI. Antidepressant Medication as a Risk Factor for Type 2 Diabetes and Impaired Glucose Regulation: Systematic Review. Diabetes Care 2013;in press.

(46) Serretti A, Mandelli L. Antidepressants and body weight: a comprehensive review and meta-analysis. J Clin Psychiatry 2010 Oct;71(10):1259-72.

(47) van der Feltz-Cornelis CM, Nuyen J, Stoop C, Chan J, Jacobson AM, Katon W, et al. Effect of interventions for major depressive disorder and significant depressive symptoms in patients with diabetes mellitus: a systematic review and meta-analysis. Gen Hosp Psychiatry 2010 Jul;32(4):380-95.

(48) van der Feltz-Cornelis CM. Comorbid diabetes and depression: do E-health treatments achieve better diabetes control? Diabetes Management 2013;3(5):379-88.

(49) Katon WJ, Von Korff M, Lin EH, Simon G, Ludman E, Russo J, et al. The Pathways Study: a randomized trial of collaborative care in patients with diabetes and depression. Arch Gen Psychiatry 2004 Oct;61(10):1042-9.

(50) Katon W, Russo J, Lin EH, Schmittdiel J, Ciechanowski P, Ludman E, et al. Cost-effectiveness of a multicondition collaborative care intervention: a randomized controlled trial. Arch Gen Psychiatry 2012 May;69(5):506-14.

(51) Disability Rights Commission. Equal Treatment: Closing the gap. A formal investigation into physical Health inequalities experienced by people with learning difficulties and mental health problems. London: Disability Rights Commission; 2006.

(52) Mitchell AJ, Malone D, Doebbeling CC. Quality of medical care for people with and without comorbid mental illness and substance misuse: systematic review of comparative studies. Br J Psychiatry 2009 Jun;194(6):491-9.

(53) Lawrence D, Coghlan R. Health inequalities and the health needs of people with mental illness. N S W Public Health Bull 2002 Jul;13(7):155-8.

(54) Frayne SM, Halanych JH, Miller DR, Wang F, Lin H, Pogach L, et al. Disparities in diabetes care: impact of mental illness. Arch Intern Med 2005 Dec 12;165(22):2631-8.

(55) Crandall JP, Knowler WC, Kahn SE, Marrero D, Florez JC, Bray GA, et al. The prevention of type 2 diabetes. Nat Clin Pract Endocrinol Metab 2008 Jul;4(7):382-93.

(56) The 10-year cost-effectiveness of lifestyle intervention or metformin for diabetes prevention: an intent-to-treat analysis of the DPP/DPPOS. Diabetes Care 2012 Apr;35(4):723-30.

(57) Rubin RR, Ma Y, Peyrot M, Marrero DG, Price DW, Barrett-Connor E, et al. Antidepressant medicine use and risk of developing diabetes during the diabetes prevention program and diabetes prevention program outcomes study. Diabetes Care 2010 Dec;33(12):2549-51.

(58) Rubin RR, Ma Y, Marrero DG, Peyrot M, Barrett-Connor EL, Kahn SE, et al. Elevated depression symptoms, antidepressant medicine use, and risk of developing diabetes during the diabetes prevention program. Diabetes Care 2008 Mar;31(3):420-6.

(59) Li C, Ford ES, Strine TW, Mokdad AH. Prevalence of depression among U.S. adults with diabetes: findings from the 2006 behavioral risk factor surveillance system. Diabetes Care 2008 Jan;31(1):105-7.

(60) Rodgers M, Asaria M, Walker S, McMillan D, Lucock M, Harden M, et al. The clinical effectiveness and cost-effectiveness of low-intensity psychological interventions for the secondary prevention of relapse after depression: a systematic review. Health Technol Assess 2012 May;16(28):1-130.

(61) Pouwer F, Tack CJ, Geelhoed-Duijvestijn PH, Bazelmans E, Beekman AT, Heine RJ, et al. Limited effect of screening for depression with written feedback in outpatients with diabetes mellitus: a randomised controlled trial. Diabetologia 2011 Apr;54(4):741-8.

(62) Nichols GA, Desai J, Elston LJ, Lawrence JM, O'Connor PJ, Pathak RD, et al. Construction of a multisite DataLink using electronic health records for the identification, surveillance, prevention, and management of diabetes mellitus: the SUPREME-DM project. Prev Chronic Dis 2012;9:E110.

(63) Lakey SL, Gray SL, Ciechanowski P, Schwartz S, Logerfo J. Antidepressant use in nonmajor depression: secondary analysis of a program to encourage active, rewarding lives for seniors (PEARLS), a randomized controlled trial in older adults from 2000 to 2003. Am J Geriatr Pharmacother 2008 Mar;6(1):12-20.

(64) de Groot M, Doyle T, Kushnick M, Shubrook J, Merrill J, Rabideau E, et al. Can lifestyle interventions do more than reduce diabetes risk? Treating depression in adults with type 2 diabetes with exercise and cognitive behavioral therapy. Curr Diab Rep 2012 Apr;12(2):157-66.

**Figure Legends**

Figure 1. Summary of Shared Pathogenic Mechanisms in the Depression-Diabetes Association covered at the International Conference on Depression and Diabetes

**Table Legends**

Table 1: Mechanisms and Pathogenesis Future Research Needs and Recommendations

Table 2: Clinical Aspects and Treatment Future Research Needs and Recommendations

Table 3: Public Health and Prevention Future Research Needs and Recommendations

Table 1: Mechanisms and Pathogenesis Future Research Needs and Recommendations

|  |  |  |
| --- | --- | --- |
| **Mechanism** | **Basic Science** | **Clinical, Behavioral, and Population Science** |
| Environmental Factors | ● Develop models of stress/depression in existing diabetic animal models to evaluate genetic and epigenetic factors, developmental stressors, and environmental stressors | ● Develop longitudinal studies to determine if neighborhood factors modify the association between depression and diabetes  ● Develop life course studies to examine the impact of cumulative early life and environmental stressors on incident depression and diabetes |
| Hypothalamic-Pituitary-Adrenal Axis | ● Design animal studies to elucidate the role of HPA axis in neuroplasticity, which has implications for development of both depression and cognitive dysfunction in the setting of diabetes. | ● Incorporation of static and dynamic measures of HPA axis function into human studies to elucidate the role of the HPA axis in depression and type 1 and type 2 diabetes.  ● Utilize uniform cortisol sampling protocols and analytic strategies across studies to allow comparability.  ● Evaluate the impact of corticotrophin releasing hormone and 11-beta hydroxysteroid dehydrogenase-1 antagonists and behavioral interventions on HPA axis function. |
| Inflammation | ● Conduct preclinical studies of diabetes and cognition/neurogenesis that incorporate measures of inflammation (e.g. acute phase proteins, IL-6, inflammatory signaling pathways including NF-kappaB and p38 MAP kinase, ratio kynurenine:tryptophan, microglia activation) and tests of depression-like behavior | ● Conduct studies to determine if anti-inflammatory strategies would be beneficial for the treatment of depression in the context of diabetes  ● Conduct association studies on biomarkers of inflammation and symptoms of depression  ● Conduct studies to determine the degree to which overlapping development conditions—personal, cultural, ecological—explain the comorbidity of diabetes and depression and how central are inflammatory processes to this overlap |
| Circadian rhythm/sleep disturbance |  | ● Conduct studies to elucidate whether the pathogenesis of depression in patients with diabetes is causally linked to obstructive sleep apnea (OSA) or whether the diabetic state is the driving force in the development of depression independent of sleep status.  ● Conduct studies to elucidate disruptions in endocrine axes and neurotransmitter pathways common to depression, diabetes, and OSA  ● Design studies to define mechanisms underlying improvement in depression that have been associated with improved glycemic control as well as improved OSA |
| Behavioral Factors | ● Conduct studies to understand neural circuitry associated with behavioral regulation in diabetes | * Evaluate linkage between self-care adherence, hyperglycemia and onset of depression in adults with T1DM and T2DM * Evaluate mechanisms associated with mood changes resulting from physical activity in adults with T1DM and T2DM * Evaluate types of physical activity and thresholds for duration and intensity to produce mood improvements in adults and children of different ages with T1DM and T2DM. |
| Treatment Factors | ● Evaluate existing antidepressant and antipsychotic medications in animal models of diabetes to determine mechanisms of action for treatment  ● Evaluate anti-hyperglycemic therapies (e.g. Glucagon-Like Peptide [GLP] agonists) as novel experimental treatment for diabetes and depression (via regulation of glycemic control [direct mechanism] and/or regulation of neuroplasticity [indirect mechanism]) | ● Design adequately powered randomized controlled trials of antidepressants which assess metabolic risk and which will allow understanding how psychotropic medications interact with other risk factors for diabetes  ● Examine existing databases for reporting possible adverse metabolic consequences of anti-depressant treatment  ● Consider the potential effects of psychotropic medication in future diabetes prevention trials  • Examine the impact of sociocultural factors on the acceptability and outcome of treatment preferably using collaborative research allowing an exchange of experience and evidence among countries |

Table 2: Clinical Aspects and Treatment Future Research Needs and Recommendations

|  |  |
| --- | --- |
| Phenomenology and Prevalence Studies | ● Clarity and specificity in future studies in measurement/definition of depressive symptoms versus depressive disorders (psychiatric diagnoses) versus diabetes distress  ● Prospective longitudinal studies of diabetes subtypes and phenotypes, especially type 1 and type 2 diabetes, to study inception predictors and comorbidity course  ● Develop cross-culturally applicable assessment instruments allowing the identification of depression comorbid with diabetes |
| Depression Screening | ● Studies to assess cost-effectiveness in depression screening in the context of intervention trials  ● Studies of electronic medical record surveillance to identify diabetic patients at high risk for depression |
| Treatment Modalities, Care Delivery, and Cost-effectiveness | **Psychotherapy**  ● Determine which psychotherapeutic approaches are most effective for which diabetes subpopulations and in different types of depressive disorders  ● Expand treatment modalities beyond cognitive behavior therapy  ○ Exercise   * Mindfulness-based stress reduction   ○ Community-based programs linking non-healthcare system resources  **Medications**  ● Evaluate mechanisms of depression medication treatments in randomized controlled trials in type 1 and type 2 diabetes  **Collaborative Care**  ● Identify methodologies and infrastructure to deliver economically sustainable, integrative collaborative care adjusted to the cultural and economic conditions prevailing in different countries and parts of countries  ● Develop technologies to extend collaborative care to patients and providers  ● Develop payment approaches to support case management at national and state level |

Table 3: Public Health and Prevention Future Research Needs and Recommendations

|  |  |
| --- | --- |
| Preventing Co-Morbid Depression and Diabetes | ● Identify and implement best practice into routine healthcare for integrated health services for co-morbid depression and diabetes in different types of service and in different countries  ● Expand economic studies of depression-diabetes co-morbidity to non-US countries  ● Incorporate non-healthcare related costs into cost-effectiveness analyses |
| Preventing Diabetes in Depression | ● Develop studies to understand the effect of depression and anti-depressants on diabetes preventive interventions  ● Determine if prevention or treatment of depression can reduce type 2 diabetes incidence  ● Validation of diabetes risk engines in individuals with depression |
| Preventing Depression in Diabetes | ● Conduct future depression intervention studies in diabetic individuals in primary and subspecialty care settings  ○ Evaluate effectiveness  ○ Target healthcare providers as intervention focus  ● Conduct health services studies to determine the optimal way of delivering depression interventions  ○ Non-professional workers (e.g. peer support)  ○ New technologies  ● Utilize alternative research methodologies to more closely model the clinical care setting (e.g. Practice Based Research Networks, pragmatic trials, systems science, longer term observational studies) |
| Primary Prevention of Depression and Diabetes | ● Develop and test in randomized trials population-based interventions to reduce etiological factors associated with co-morbid diabetes and depression, within and across cultures and countries |