Long-term effects of a Collaborative Care Model on Depressive Symptoms and Metabolic Outcomes in India: The INDEPENDENT Randomized Clinical Trial

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Abstract

Long-term Effects of a Collaborative Care Model on Depressive Symptoms and Metabolic Outcomes in India: The INDEPENDENT Randomized Clinical Trial

Background: Chronic diseases are responsible for 60% of deaths worldwide. Multiple chronic conditions, such as comorbid type 2 diabetes (T2D) and depression, are increasingly prevalent and are made worse by fragmented medical care. Fragmented medical care is a major barrier to the treatment of multiple chronic conditions in low-and-middle income countries, such as India. This study examined the long-term effects of a collaborative care model on metabolic indicators and depressive symptoms among adults in India with poorly-controlled T2D and comorbid depression.

Methods: The Integrating Depression and Diabetes Treatment (INDEPENDENT) trial was a multicenter, open-label, pragmatic clinical trial comparing a 12-month active collaborative care intervention with usual care for patients with poorly-controlled diabetes and comorbid depression. At baseline, 404 patients at 4 clinic sites were randomized. At 36-months following randomization, N = 331 intervention participants (n=156 collaborative care model and n=175 usual care) were assessed for target outcomes. Long-term intervention effects were estimated at 36-months as risk differences and risk ratios comparing the collaborative care group to the usual care group on the primary composite outcome, comprised of ≥50% improvement in the 20-item Symptom Depression Checklist (SCL-20) scores since baseline and one or more of the following: 0.5-percentage point reduction in HbA1C, 5 mmHg or more reduction in SBP, or a 10 mg/dL reduction in LDL cholesterol. Secondary outcomes included change since baseline in HbA1c, SBP, LDL, and SCL-20, separately. We also evaluated heterogeneity in treatment effects by socioeconomic and health characteristics at baseline.

Results: At 36-months, among 331 patients randomized (mean [SD] age: 52.6 [8.4]; 207 [62.5%] female), there was not a statistically significant difference between the percentage of patients who attained the primary outcome in the collaborative care group vs. usual care group (62.1% vs. 57.8%; RD, 4.3 [95% CI: -6.2%-1.5%]; RR: 1.07 [95% CI: 0.90, 1.27]).

Conclusion: At 36 months following randomization, there were no improvements in metabolic parameters or depressive symptoms associated with a proven-effective collaborative care model. Continued active intervention may be needed to achieve sustained control of metabolic disease and depression in low-resource settings.

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Chapter I: Introduction

Non-communicable diseases are complicated to prevent, treat, and manage because they are time-intensive, costly, and rely on coordinated care to successfully manage. Type 2 diabetes is one such NCD that is difficult to manage due to the necessary blood sugar monitoring, administration of medications (e.g., insulin) and diet control that is required. There has been a ubiquitous, global rise in the prevalence of T2D and it now ranks among the top 10 causes of death in the world (*The Top 10 Causes of Death*, n.d.). The prevalence of T2D has increased substantially in India over the last 30 years; almost 12% of urban populations now have the disease (Ramachandran, 2002). India also has the largest number of cases of T2D in the world, numbering at over 100 million (Mehta et al., 2009).

Depression is another NCD that has risen substantially throughout the world in the last few decades. Globally, depression is the most common mental health condition and over 250 million people have the condition at any one time (Liu et al., 2020). In India, 45.7 million people were estimated to have depression in 2017. Depression is treatable but requires medical recognition and medication and/or lifestyle intervention to lower the burden of symptoms. However, depression diagnoses are often missed due to inadequate physician training, a shortage of mental health-trained professionals, and/or social stigma (Sagar et al., 2020). Additionally, T2D and depression are bidirectional and exacerbate each other in terms of severity when they are co-occurring (Patel & Chatterji, 2015).

Both T2D and depression are treatable and manageable conditions, but the fragmented medical system in India makes it difficult for patients with both conditions to manage their diseases. India largely has a fragmented medical system that places much of the burden of

navigating care on patients and their caregivers, making the treatment and management of NCDs impractical for many patients (Yellapa et al., 2017). Additionally, there is less than one physician per 1,000 people in India and this number decreases with chronic disease physicians and psychiatrists (Garg et al., 2019; *Physicians (per 1,000 People) - India | The World Bank Data*, n.d.). Additionally, the evidence-to-date of interventions and care models to address these comorbid diseases are almost exclusively in high-income countries.

To address the gaps in care for chronic disease generally and depression specifically, the Integrating Depression and Diabetes Treatment (INDEPENDENT) study sought to investigate the effectiveness of collaborative care models to address T2D and depression in low-and-middle income countries (LMICs), such as India (Ali et al., 2020; Kowalski et al., 2017). At the end of a year-long active intervention period and at 12 months following active intervention, there was a significantly greater percentage of patients in the intervention group vs the usual care group who met the primary outcome (71.6% vs 57.4%; Risk Difference, 16.9% [95% CI: 8.5%-25.2%]) (Ali et al., 2020). In the present study, we investigate the extent to which favorable outcomes were observed 12 months after the conclusion of the primary trial, that is, 36 months following randomization and 24 months after the end of active intervention.

Chapter II: Literature Review

The Epidemiologic Transition in India

India is one of the most ethnically, linguistically, religiously, and geographically diverse countries in the world (*India - The World Factbook*, n.d.). India is home to 1.37 billion people and the country continues to grow in population, power, energy, and cultural influence (Chandrashekar, 2019). Since gaining independence in 1947 from avaricious Britain, India has made immense progress in lowering death and disability due to respiratory infections (e.g., tuberculosis), maternal complications, neonatal complications, malaria, and enteric infections; even more accelerated progress has occurred since 1990 (*Non-Communicable Diseases | National Health Portal Of India*, n.d.). With the continued, lower contribution of infectious diseases to the disease burden, there has been a rapid rise in the prevalence of non-communicable diseases (NCDs), such as heart disease, stroke, type 2 diabetes (T2D), cancers, depression, and substance abuse (*GBD Compare | IHME Viz Hub*, n.d.). This epidemiologic transition has generated much awareness and attention to chronic conditions such as diabetes and depression (Dandona et al., 2017).

Global Burden of Type 2 Diabetes

Type 2 diabetes (T2D) is the 8th leading cause of death in the world. The contribution of type 2 diabetes to overall disease burden has been rapidly rising, with an almost-double increase from 12.37 deaths per 100,000 persons in 1990 to 20.05 deaths per 100,000 persons in 2019. Approximately 1.6 million deaths were directly attributable to T2D in 2016 (*GBD Compare | IHME Viz Hub*, n.d.). Although T2D is sometimes thought of as a condition largely affecting populations in high income settings, data show that almost two-thirds of the T2D burden occurs in low-and-middle income countries (LMICs) (Tabish, 2007). India has the largest number of

recorded cases of T2D in the world, which number to over 100 million; the estimated prevalence of T2D in the country is up to 12% in urban areas (Mehta et al., 2009).

T2D is a chronic disease that is characterized when the human pancreas does not produce enough insulin or use insulin efficiently. Hyperglycemia, or raised blood sugar, can result in organ damage, nerve damage, vision loss, blood vessel disrepair, and death. T2D is caused by physical inactivity, obesity, unhealthy diet, and tobacco use (*Diabetes*, n.d.). Chronic conditions such as obesity, hypertension, heart disease, stroke, depression, and high cholesterol all contribute to higher odds of developing T2D (*IDF Diabetes Atlas 9th Edition 2019*, n.d.). Although the rise in prevalence in T2D-realted mortality and morbidity is concerning, the disease is not uncurable and can be managed with medication and lifestyle behavior changes. Additionally, screening for sub-clinical prediabetes and medication adherence T2D are important to preventing and managing the disease, respectively (CDC, 2020).

Medications, lifestyle behavior change (i.e., healthy diet and regular physical activity), and screening are well-documented in lowering T2D risk factors and can even prevent T2D altogether (*IDF Diabetes Atlas 9th Edition 2019*, n.d.). Programs such as the U.S. National Diabetes Prevention Program (DPP), Indian Diabetes Prevention Programme, the Australian National Diabetes Services Scheme, and diabetes prevention programs in China are just a few examples of national/state programs that combine strategies of mediation adherence, lifestyle behavior change (e.g., physical activity, diet change, tobacco cessation), and regular screenings to prevent and manage T2D (*Diabetes Prevention Programme WDF05-108*, 2012; *National Diabetes Prevention Program | Diabetes | CDC*, 2019; *Prevention – Diabetes Australia*, n.d.; Ramachandran et al., 2006). The U.S. National DPP, for example, has shown evidence of short-term (e.g., 6 months) and long-term effectiveness (e.g., 3 years) in preventing T2D among those

with pre-diabetes in a variety of settings (e.g., rural, urban), delivery methods (e.g., in-person, distance learning), and payors (e.g., Medicaid) ("A National Effort to Prevent Type 2 Diabetes: Participant-Level Evaluation of CDC's National Diabetes Prevention Program," 2017; "Reduction in the Incidence of Type 2 Diabetes with Lifestyle Intervention or Metformin," 2002; Diabetes Prevention Program Research Group et al., 2009). For those already with T2D, and those with T2D and comorbid diseases (e.g., depression), the long-term effects of lifestyle and medication interventions are less well-known; the current literature establishes that these interventions confer positive, short-term effects in more effective management of the conditions and increased quality of life among patients (Ghaeli et al., 2004; P. J. Lustman et al., 1997; Patrick J. Lustman et al., 2006, 2007).

Global Burden of Depression

The Global Burden of Disease Study (2017) estimates that over 264 million people live with depressive disorders (depression). Depression is one of the leading causes of non-communicable disease morbidity and represented 1.84% of all DALYs in 2019 (*GBD Compare | IHME Viz Hub*, n.d.). Depression is a mental disorder that is characterized by changes in mood or interest, altered appetite, loss of energy, feelings of hopelessness or guilt, lack of concentration, physical aches, and/or, most concerningly, suicidal thoughts (*Depression | NAMI: National Alliance on Mental Illness*, n.d.). Depression is prevalent in every population throughout the world and is associated with social stigmatization in most populations and cultures (*Depression*, n.d.; Yokoya et al., 2018). Trauma, genetics, life stressors, drug/alcohol misuse, and other conditions can contribute to a higher risk of depression (*Depression | NAMI: National Alliance on Mental Illness*, n.d.). Identification of depression and depressive symptoms can often be missed or skipped over in clinical settings, which is one of the main challenges of

managing the condition (Falconer et al., 2018). EMR prompts for clinicians as a reminder to screen for depression is an empirical solution to remedy this problem (Carroll et al., 2013). Depression can be treated and managed with psychoeducation, nutritional changes, psychotherapy, medication, and lifestyle modification (Cuijpers et al., 2012).

The Global South faces high rates of untreated depression, with an estimated 76-85% of cases going without attention; untreated depression can lead to extremely adverse events, such as self-harm or suicide (Wang et al., 2007). In India, 45.7 million people were estimated to have depression in 2017; depression contributed to one-third (33.8%) of DALYs associated with mental disorders in the country (Sagar et al., 2020).

Impact of Comorbid Type 2 Diabetes & Depression

Chronic diseases like type 2 diabetes, heart diseases, and cancers are associated with depression and contribute to worse outcomes mentally, emotionally, and physically for a person with these comorbid combinations (Simon, 2001). The incidence of multiple chronic conditions (MCCs) has risen in the last twenty years, further complicating the needs of patients (Hajat & Stein, 2018). The rise in MCCs necessitates creative, cross-collaborative, and cost-effective solutions.

T2D and depression are bidirectional, meaning that people with T2D are more likely to experience depression compared to those without T2D; depression among patients with T2D is associated with a decreased extent to which diabetes self-monitoring guidance is followed, such as dietary modification, physical activity, medication compliance, and/or blood glucose monitoring (Alzoubi et al., 2018; CDC, 2018; Moussavi et al., 2007). Comorbid T2D and depression is also associated with more severe T2D outcomes (e.g., retinopathy, neuropathy); additionally, the psychosocial intensity that T2D treatment requires is associated with recurrent,

episodic depression (Katon, 2008). Recent research also indicates that people with comorbid T2D and depression results in higher cost of care (i.e., financial burden) compared to people with just one of these conditions (Egede et al., 2002). Although not in the scope of this study, it is important to recognize that the COVID-19 pandemic has exacerbated depression and other psychological distress among persons with T2D (Alessi et al., 2020; Vahratian, 2021). Chronic conditions, such as T2D, are associated with higher mortality and severe outcomes from COVID-19 disease (Razzaghi, 2020).

Access to Medical Care for Chronic Conditions

Suboptimal healthcare access and quality accounts for up to 10-15% of worldwide deaths (National Academies of Sciences, Engineering, and Medicine, 2018). Even though empirical and effective solutions exist for treating both T2D and depression, suboptimal quality of healthcare prevents medication access, proper and timely screenings, and/or provider-patient interaction necessary for medical, behavioral, and/or educational intervention. Barriers to effective care include long distances/transportation burden, stigma, and limited resources (e.g., financial strain, shortage of health professionals) (Jacobs et al., 2012). Fragmented medical care is also affected by social factors and the social determinants of health, such as food insecurity, unsafe/unsanitary housing, poverty, racism, colorism, classism, sexism, and limited education (*Social Determinants of Health*, n.d.; *Social Determinants of Health | CDC*, 2021).

Globally, care for mental health is particularly impacted by the shortage of health workers trained in mental health (*WHO | WHO's Mental Health Atlas 2017 Highlights Global Shortage of Health Workers Trained in Mental Health*, n.d.). In India, there are an estimated 0.75 psychiatrists per 100,000 persons while the saturation number is 3 or greater per 100,000 persons (Garg et al., 2019).

Treatment and management of comorbid T2D and depression is an ongoing field of research and intervention (Rubin et al., 2004). Most interventions to address comorbid T2D and depression have focused on using T2D medications or SSRIs (i.e., medications to treat depression) to see if there is effectiveness in treating the comorbid condition while also effectively treating the intended condition (Ghaeli et al., 2004; P. J. Lustman et al., 1997; Patrick J. Lustman et al., 2006). Results from these studies show improvements in clinical outcomes for T2D and depression together. There have also been a few studies that focus on enhanced care or collaborative care (Kinder et al., 2006; Lin et al., 2006). Watson et al. (2013) conducted a meta-analysis of the effectiveness of practice-based interventions for improving depression and chronic medical outcomes – findings conferred that collaborative care models improved depression and quality of life indicators among patients after six months (Watson et al., 2013). Huang et al. (2013) conducted a systematic review and meta-analysis of collaborative care interventions for patients with comorbid T2D and depression; the authors found statistically significant improvements in depression treatment response, depression remission, and T2D and depression medication adherence (Huang et al., 2013).

Many of these studies have only followed up with patients in the short-term, the shortest with final endpoints of eight weeks and the longest follow-up time being only one year after study start. There are gaps in our understanding of the effectiveness of interventions to treat comorbid T2D and depression in the long-term to see if effects are sustained over time. Additionally, all the studies took place in the Global North (and mostly in the U.S.), despite the concentrated burden of chronic conditions in the Global South (*Non Communicable Diseases*, n.d.).

The INDEPENDENT Trial

The Integrating Depression and Diabetes Treatment (INDEPENDENT) study was a parallel, open-label, pragmatic randomized control trial (RCT) conducted across four diabetes clinics in India from 2015 to 2019. The trial targeted patients with poorly controlled diabetes and signs of depression. The objective of the INDEPENDENT study was to investigate the sustained effects of a collaborative care model to treat and manage T2D and depression in diabetes clinics in India. The intervention was a collaborative care model for depression and diabetes which consisted of self-management support from care coordinators; routine case reviews with mental health specialists; and clinical decision support embedded within patient electronic health records to aid attending physicians with patient management decisions.

In the primary trial, participants in the intervention group received a year (12 months) of the collaborative care model; these participants were then followed up for an additional 12 months without intervention (i.e., usual care). The control group received usual care for the entire 24-month period. The primary study reported the effectiveness of the intervention among participants at 12 months and 24 months after randomization. Investigators observed statistically significant improvements in a composite measure of depressive symptoms and cardiometabolic indices at 12 and 24 months (Ali et al., 2020). Further details on the INDEPENDENT study design and complete trial results have been previously published (Ali et al., 2020; Kowalski et al., 2017).

Chapter III: Manuscript

Long-term Effects of a Collaborative Care Model on Depressive Symptoms and Metabolic Outcomes in India: The INDEPENDENT Randomized Clinical Trial

Abstract

Importance: Diabetes and depression are commonly occurring comorbidities that are increasingly prevalent in low- and middle-income countries. Management for these conditions is complex and is constrained by the lack of mental health specialists.

Objective: To determine if collaborative care vs. usual care improved metabolic indicators and lowered depressive symptoms among adults in India with comorbid type 2 diabetes and depression 36 months after enrollment in the Integrating Depression and Diabetes Treatment (INDEPENDENT) trial.

Design: Parallel, open-label, pragmatic randomized clinical trial.

Setting: Four diabetes clinics in India (three private, one public) located in different areas of the country.

Participants: Patients with type 2 diabetes (T2D) with a patient health questionnaire (PHQ-9) score of at least 10 (range, 0-27) *and*: hemoglobin A1c (HbA1c) of at least 8%, systolic blood pressure (SBP) of at least 140mmHg, or low-density lipoprotein (LDL) cholesterol of at least 130mg/dL.

Exposure(s): Collaborative care model vs. usual care.

Main Outcome(s) and Measure(s): The primary outcome was between-group difference in the percentage of patients at 36 months with ≥50.0% improvement in SCL-20 scores from baseline

and one or more of the following: 0.5-percentage point reduction in HbA1C, 5 mmHg or more reduction in SBP, or a 10 mg/dL reduction in LDL cholesterol from baseline.

Results: There was not a statistically significant difference in the percentage of patients achieving the primary outcome at 36 months between the collaborative care vs. usual care (62.1% vs. 57.8%; RD, 4.3 [95% CI: -6.2%-1.5%]; RR: 1.07 [95% CI: 0.90, 1.27]).

Conclusion and Relevance: At 36 months following randomization, there were no improvements in metabolic parameters or depressive symptoms associated with a proven-effective collaborative care model. Continued active intervention may be needed to achieve sustained control of metabolic disease and depression in low-resource settings.

Key Points

Research Question: Among patients with poorly-controlled diabetes and depression in India, does a 12-month collaborative care intervention improve depressive symptoms and measures of cardiometabolic health more than usual care at 36 months?

Findings: There was not a statistically significant difference in the percentage of patients with the composite, primary outcome (i.e., patients who had at least 50% improvement in SCL-20 scores and at least one of the following: at least 0.5-percentage point (ppt) reduction in HbA1c, at least 5-mm Hg reduction in SBP, or at least 10-mg/dL reduction in LDL cholesterol at 36 months) at 36 months between the collaborative care vs. usual care group (62.1% vs. 57.8%; RD, 4.3 [95% CI: -6.2%-1.5%]; RR: 1.07 [95% CI: 0.90, 1.27]).

Meaning: Among patients with T2D and depression in India, a collaborative care model did not result in improvements in a composite measure of cardiometabolic indicators and depression outcomes at the 36-month time point (i.e., 24 months after intervention ended). The null effects at 36 months contrast with statistically significant differences between the two groups at the 24-month follow-up (i.e., 12 months after intervention end). This difference may indicate a need for continued collaborative care interventions to achieve sustained control of comorbid chronic conditions over the long term.

Introduction

Type 2 diabetes (T2D) is the 8th leading cause of death in the world (*GBD Compare | IHME Viz Hub*, n.d.). The contribution of type 2 diabetes to overall disease burden has been rapidly rising, with an almost-double increase from 12.37 deaths per 100,000 persons in 1990 to 20.05 deaths per 100,000 persons in 2019. India has the largest number of recorded cases of T2D in the world, which number to over 100 million; the estimated prevalence of T2D in the country is up to 12% in urban areas (Mehta et al., 2009). Although the rise in prevalence in T2D-realted mortality and morbidity is concerning, the disease is not uncurable and can be managed with medication and lifestyle behavior changes.

Over 264 million people live with depressive disorders (depression). Depression is one of the leading causes of non-communicable disease morbidity and represented 1.84% of all DALYs in 2019. In India, 45.7 million people were estimated to have depression in 2017; depression contributed to one-third (33.8%) of DALYs associated with mental disorders in the country (Sagar et al., 2020).

T2D and depression are bidirectionally associated (Patel & Chatterji, 2015). People with T2D are more likely to experience depression compared to those without T2D, and depression is a risk factor for the development of diabetes. Moreover, depression may impact control of diabetes. Depression among patients with T2D is associated with a decreased extent to which diabetes self-monitoring guidance is followed, such as dietary modification, physical activity, medication compliance, and/or blood glucose monitoring (Alzoubi et al., 2018; CDC, 2018; Moussavi et al., 2007). Comorbid T2D and depression is also associated with more severe T2D outcomes (e.g., retinopathy, neuropathy).

Even though effective strategies exist for treating both T2D and depression, suboptimal quality of healthcare prevents guideline-based medical management, routine monitoring of metabolic parameters, and provider-patient interaction necessary for medical, behavioral, and/or educational intervention. Principal barriers to effective management of comorbid diabetes and depression within the healthcare system include difficult-to-navigate clinics, clinical inertia, and the critical shortage of mental health specialists (e.g., physiatrists, therapists) in India (Garg et al., 2019).

The WHO has supported integrated care as effective and realistic to increase access to mental health services while also being treated for other conditions (*WHO | Integrating the Response to Mental Health Disorders and Other Chronic Diseases in Health Care Systems*, n.d.). The Integrating Depression and Diabetes Treatment (INDEPENDENT) trial was designed to investigate the effects of a 12-month collaborative care model to treat and manage T2D and depression in diabetes clinics in India. A higher proportion of participants in the collaborative care group (vs. usual care) achieved a composite cardiometabolic and depression care goal 12 months (1 year) and 24 months (2 years) after randomization (Ali et al., 2020).

In this study, we seek to investigate the effects of the collaborative care model vs. usual care 36 months (3 years) after randomization. The analysis contributes an understanding of long-term effectiveness of a collaborative care model addressing comorbid T2D and depression in India.

Methods

Intervention Components & Study Population

The INDEPENDENT study was a parallel, open-label, pragmatic randomized control trial (RCT). The four intervention components included:

1) Notification to the provider of depression status.

2) Care Coordination: Care coordinators were nutritionists—without prior mental health expertise—who were trained to support and stimulate patient care through provision of educational materials, trainings to patients for diabetes self-monitoring, and helping patients and patients' families set goals. These care coordinators also followed-up with patients frequently about achieving their goals (i.e., motivational interviewing).

3) Decision-Support Electronic Health Record (DS-EHR): Clinical decision support prompts were embedded within patient electronic health records. The decision support advises clinicians on medical management of glucose, blood pressure, lipid, and depression. The DS component assists clinicians in providing responsive therapy suggestions and delivering guideline-based prompts, while the EHR component tracked, and prioritized patients based on highest needs.

4) Case Reviews: There were weekly case reviews of patients between a diabetologist and a remote mental health specialist (e.g., psychiatrists) to make coordinated decisions. Care coordinators also attended and participated in these weekly case reviews.

Participants in the intervention group were treated for a year (12 months) using the collaborative treatment model. The control group received usual care with provider notification of patient depression status during the 12-month intervention period. Patients in both arms were assessed every 6 months, and between-group outcomes were evaluated at 12 months following the conclusion of active intervention (i.e., 24 months after randomization).

Recruitment and Randomization

The trial was conducted at four diabetes clinics across India over a 36-month period – these sites included New Delhi, Chennai, Bangalore, and Visakhapatnam. An interactive map of study sites with geographic location in India, a description of the site, and location pictures are available on Google Earth at this link. Patients were eligible for inclusion if they were 35 years or older, had type 2 diabetes, moderate-to-severe depression (PHQ-9 score ≥ 10), and one or more uncontrolled cardiometabolic indicator (hemoglobin A1c [HbA1c] ≥8%, systolic blood pressure (SBP) ≥140mmHg, or low-density lipoprotein (LDL) cholesterol≥130mg/dL) (***Figure 1***). Patients were screened and enrolled from March 9th, 2015, to May 31st, 2016. The final 36-month visit was completed on December 6th, 2019. Site investigators reviewed clinic site records to identify patients with elevated HbA1c, SBP, and/or LDL cholesterol values and referred these patients to be screened for depressive symptoms using the PHQ-9. Patients with alcohol or substance use disorders, cognitive disorders, bipolar or psychotic disorders, type 1 diabetes, kidney failure, or cardiovascular disease (CVD) events in the past 12 months (myocardial infarction, unstable angina, or stroke) were excluded.

Patients were randomly assigned to either the collaborative care model (intervention) or usual care (control) via a password-protected web data management system called the Interactive Web Response System. Patients were randomized in blocks of 4, 6, 8, or 10, by site, and randomization was communicated by the coordinating center of the site.

Assessments

Patients were assessed at baseline, six months, twelve months, eighteen months, twenty-four months, and thirty-six months. The data collection instruments were designed to collect demographic data (e.g., gender), household characteristics (e.g., income), clinical and lab metrics

(e.g., A1C), health information (e.g., family history of type 2 diabetes), and social variables (e.g., primary language). Of the 453 people who were eligible, 404 patients consented and were enrolled in the trial.

Neither patients nor providers could be realistically blinded to treatment randomization (per the nature of the intervention). However, the study assistants (who collected patient data) remained blinded throughout the entire study.

Additional details about intervention components, trial protocols, and randomization were published elsewhere in Ali et al. (2020) and Kowalski et al. (2017).

Outcomes

Between-Group, Mean, and Risk Differences

The primary outcome for this study was the between-group difference in the unadjusted percentage of patients who had at least 50% improvement in SCL-20 scores and at least one of the following: at least 0.5-percentage point reduction in HbA1c, at least a 5-mm Hg reduction in SBP, or at least 10-mg/dL reduction in LDL cholesterol at 36 months.

Secondary outcomes were the 36 month between-group differences in: the percentage of patients who met treatment targets (HbA1c <7.0%, SBP <130 mm Hg, LDL cholesterol <100 mg/dL [<70 mg/dL if history of CVD]) or had significant reductions in individual outcomes (at least a 50% reduction in SCL-20 score, ≥0.5-percentage point reduction in HbA1c, at least a 5-mm Hg reduction in SBP, and at least a 10-mg/dL reduction in LDL cholesterol); the percentage of patients who met HbA1c, SBP, and LDL cholesterol targets together; and mean changes in SCL-20 score, PHQ-9 score, HbA1c, SBP, and LDL cholesterol.

We also examined the primary outcome at 36 months by socioeconomic and clinical characteristics; these characteristics were age, sex, education, household income, duration of diabetes, and study site.

Common Effect Outcome

To assess whether the intervention had similar, beneficial effects on SCL-20 scores, HbA1c, SBP, and LDL, we constructed a measure of "common effect". We standardized all four continuous measures to be centered at a mean of zero with standard deviation of one (i.e., the standard normal distribution). The normalization allows comparison of outcomes on the same scale.

Statistical Analysis

Patient characteristics and clinical measurements were described by treatment assignment at baseline. We estimated the risk differences (RDs) for achieving the primary outcome and secondary outcomes between the collaborative care group and usual care group at 36 months and accounted for treatment status and site location; the RDs were estimated using linear probability models with an identity link. We also estimated risk ratios (RRs) for the primary outcome and all secondary outcomes using log-binomial regression. The between-group mean differences of secondary outcomes were also estimated using linear regression. We estimated the RDs and RRs in intervention effects of the collaborative care group vs. usual care group by age, sex, education, household income, duration of diabetes, and study site. All point estimates are shown with 95% confidence intervals and p-values (alpha = 0.05).

We also conducted a post-hoc analysis comparing the mean SCL-20, LDL, HbA1c, and SBP scores of participants at baseline and 36 months.

As a supplemental analysis, we evaluated differences in characteristics of participants who were retained in follow-up at 36 months after randomization (N=331) and those lost to attrition (N=73).

All analyses were conducted using SAS statistical software version 9.4. Figures were constructed using R statistical software.

Results

Of the 404 participants enrolled and randomized in the Integrating Depression and Diabetes Treatment (INDEPENDENT) study, 331 were retained in post-intervention follow-up at 36-months (i.e., 73 patients were lost to follow-up at 36-month follow-up). Compared to participants who did not complete the 36-month assessment, participants who were assessed at 36 months were more likely to be female, less educated, be employed without formal training or have a housewife occupation and have no history of cardiovascular disease (***Supplemental Table 1)***.

Patients in the collaborative care group (N=156) vs. usual care (N= 175) retained in follow-up at 36 months had similar baseline characteristics. The mean (SD) age in the collaborative care group vs. usual care group was 52.8 (8.0) years and 52.5 (8.9) years, respectively. A higher proportion of patients in both the collaborative care group and usual care group were female (55.8% and 68.6%, respectively), married (84.6% and 84.0%, respectively), completed secondary or primary education (70.5% and 68.0%, respectively), was a housewife (47.4% and 59.4%, respectively), and did not have health insurance (84.6% and 80.6%, respectively). Patients had diabetes for a mean (SD) of 8.9 (7.0) years and 9.6 (7.3) years, respectively; about a third of patients in each group were using insulin (34.0% and 34.3%, respectively), half were using blood pressure medication (48.6% and 48.9%, respectively), and a

small proportion of patients had a history of cardiovascular disease (3.2% and 4.0%, respectively). The mean (SD), baseline SCL-20 score was 25.5 (10.5) and 27.4 (10.9); LDL, 101.7 (38.3) and 104.3 (37.8); SBP, 132.0 (17.8) and 131.5 (17.8); and HbA1c, 9.3 (1.9) and 9.0 (1.8) (***Table 1***).

There was not a statistically significant difference in the percentage of patients with the composite primary outcome at 36 months between the collaborative care vs. usual care group (62.1% vs. 57.8%; RD, 4.3 [95% CI: -6.2%-1.5%]; RR: 1.07 [95% CI: 0.90, 1.27]).

With respect to secondary outcomes, we assessed 4 binary outcomes, 4 composite measures, and 6 continuous measures of depressive symptoms and/or metabolic health. At 36 months after randomization, we observed statistically significant improvement in 1 of 4 single measure in the collaborative care group compared to the usual care group (52.9% vs. 42.1% 0.5-percentage point reduction in HbA1c for the intervention versus control group, respectively; RD, 10.0 [95% CI: -0.3%-2.1%], RR, 1.26 [95% CI: 1.00, 1.56]). There were no statistically significant between-group differences in SCL-20, SBP, or LDL at the 36-month time point (***Figure 2*** and ***Table 2***).

Of 4 composite measure secondary outcomes, there were no statistically significant between-group differences at 36 months in the percentage of patients achieving any of the following: at least a 0.5-percentage point reduction in HbA1c *or* HbA1c < 7%; at least a 5-mm Hg reduction in SBP *or* a SBP <130 mm Hg; at least a10-mg/dL reduction in LDL *or* LDL <100 mg/dL (<70 mg/dL with history of CVD); HbA1c < 7%, SBP < 130 mm Hg, *and* LDL <100 mg/dL (< 70 mmHg with history of CVD) (***Table 2***).

Of 5 continuous measures of cardiometabolic and depressive indices, there were no statistically significant mean differences between the collaborative care group and usual care group in the following: SCL-20, score; PHQ-9, score; HbA1c, %; SBP, mmHg, LDL, mg/dL (***Table 2***).

There were no statistically significant heterogeneity in intervention effects on the primary outcomes at 36 months by age, sex, education level, household income, duration of T2D, or by site. While site may appear to be statistically significant in ***Table 3***, this can be attributed to interaction between the site and treatment; however, there was no between-group differences that conferred statistical significance (***Table 3***).

Post-hoc analysis comparing study outcomes at baseline and 36 months revealed that while between-group differences were null for all measures, there was a substantial reduction in overall SCL-20 scores in both groups since baseline. For SCL-20 scores, there was a mean (SD) of 25.5 (10.5) for collaborative care and 27.4 (10.9) for usual care at baseline and 7.9 (6.4) for collaborative care and 8.8 (6.5) for usual care at 36 months. For LDL, HbA1c, and SBP, average values in both groups at 36 months were no different from the time of randomization (***Figure 3***).

Lastly, there was no statistically significant common effect of the collaborative care model on SCL-20 score, HbA1c, SBP, and LDL at 36-months (0.0434 [95% CI: -0.0880-0.1749]) (***Supplemental Table 2***).

Discussion

This study examined the long-term effects of a 12-month collaborative care intervention tailored to patients with poorly controlled diabetes and depressive symptoms attending urban (private and public) clinics in India. Three years after randomization and two years after active

intervention ended, there were almost no statistically significant differences between the patients randomized to the collaborative care group vs. the usual care group with regards to cardiometabolic and depression indices.

At the conclusion of the parent trial, Ali et al. (2020) found that there were statistically significant effects of the intervention the primary outcome and some secondary outcomes at both 12 and 24 months. Between 12 and 24 months, the differences between the two groups narrowed. These differences narrowed even further at 36 months to the point where differences between groups were statistically undetectable.

Although there were no statistically significant differences found between groups, there were still clinically meaningful achievements found in both groups. The collaborative care group and usual care groups both had a high proportion of patients achieving at least a 50% improvement in SCL-20 score at 36 months (72.4% and 69.7%, respectively). Based on post-hoc analyses of single endpoints, it appears that reductions in SCL-20 scores in both groups may be the driving force behind the achievement of the primary outcome in over two-thirds of all trial participants. Mean SCL-20 scores for both the collaborative care group and usual care group at 36 months was much lower than at baseline. The common improvements in depressive scores in both groups may be a product of genuine intervention effects, social desirability bias, regression to the mean, or a combination of all three (Grimm, 2010). In both groups of patients, the provider was notified of the patient's depression status; in clinics where non-regular screening for depression was occurring, the intervention component of notifying the provider of the patient's depression status might have prompted more action from the provider and thereby, an increased perception of visibility and legitimacy of diagnosis from the patient.

In contrast to depressive symptoms, cardiometabolic indices measured at 36 months appeared to return to approximately baseline, pre-intervention values for both groups. There was a statistically significant improvement observed in the collaborative care group compared to the usual care group for the percentage of patients who had at least a 0.5-perccentage point reduction in HbA1c at 36 months. However, the mean HbA1c for the collaborative care group at 36 months (mean: 9.1% (SD: 5.9%)) is clinically similar to the HbA1c for this group at baseline (mean: 9.3% (SD: 1.9%)). These findings corroborate similar studies that have also found a return to baseline for cardiometabolic indices after long-term follow-up with comparable interventions to that of the collaborative care model in INDEPENDENT (Katon et al., 2004; McAdam-Marx et al., 2015; Sandbæk et al., 2014). These findings further underscore the need for creative and cost-effective collaborative care models that are sustainable and ubiquitously attainable during the entire period of life in which a patient may have debilitating, comorbid diseases.

The strengths of this study include a randomized trial design, standardization of measures across sites, and the novelty of the study population for the outcomes measured. Additionally, the results from this trial may be generalizable to adults with T2D and depression in urban India and other urban contexts in other LMICs.

There were also limitations to this study. Namely, the study sample was too small to identify the effects of individual intervention components. Additionally, these results are only applicable to adults with T2D and depression in urban clinics in India, meaning the intervention effects may not transfer if applied in rural settings and/or other countries.

The difference in sustainability of outcomes in this trial warrants larger trials in which differences in the effects of individuals intervention components can be detected. India has a

severe shortage of mental health professionals. It may be possible that we can leverage diabetologists, other chronic disease care providers, and the use of electronic health record prompts and decision support systems without the need for massive growth in the accrual of persons who are specifically trained in mental health to implement and sustain T2D and depression care models (Garg et al., 2019). Understanding the most effective points of care will be important in designing and implementing future collaborative care models within health systems in low-resource settings.

Conclusions

There was not a statistically significant between-group difference in the percentage of patients with a primary, composite outcome for cardiometabolic and depressive symptom control at 36-months following enrollment in a proven-effective collaborative care model for diabetes and depression treatment. The lack of between-group differences may be due to a combination of treatment effect attenuation over time in the absence of sustained intervention and secular improvements in depression over time in both groups. The reasons for the lack of between-group differences warrants further research in how to sustain interventions in to affect meaningful and lasting change among patients with comorbid T2D and depression in low-and-middle income healthcare contexts.

Tables and Figures

Table 1. Baseline Characteristics of Participants Assessed at 36 Months (N=331)

		Collaborative Care Group (N = 156)	95% CI	Usual Care Group (N = 175)	95% CI	p-value
Demographic Characteristics, % or mean (SD)						
Sex	Female	55.8	[47.9, 63.6]	68.6	[61.7, 75.5]	0.017
	Male	44.2	[36.4, 52.1]	31.4	[24.5, 38.3]	
Age, mean (SD)		52.7 (8.0)	[51.4, 53.9]	52.5 (8.9)	[51.2, 53.8]	0.1788
Marital Status	Married	84.6	[78.9, 90.3]	84.0	[78.5, 89.5]	0.555
	Single	1.9	[0.0, 4.1]	0.6	[0.0, 1.7]	
	Divorced/Separated	0.6	[0.0, 1.9]	1.7	[0.0, 3.6]	
	Widowed	12.8	[7.5, 18.1]	13.7	[8.6, 18.8]	
Education	Post-secondary	17.3	[11.3, 23.3]	20.6	[14.6, 26.6]	0.75
	Secondary or primary school	70.5	[63.3, 77.7]	68.0	[61.1, 74.9]	
	Less than primary school or unsure	12.2	[7.0, 17.3]	11.4	[6.7, 16.2]	
Occupation	Employed, training	40.4	[32.6, 48.1]	28.6	[21.8, 35.3]	0.166
	Employed, no training	5.8	[2.1, 9.4]	4.0	[1.1, 6.9]	
	Housewife	47.4	[39.6, 55.3]	59.4	[52.1, 66.7]	
	Retired	5.8	[2.1, 9.4]	6.9	[3.1, 10.6]	
	Unemployed	0.6	[0.0, 1.9]	1.1	[0.0, 2.7]	
Household Income, INR	< 3000	3.2	[0.4, 6.0]	2.3	[0.1, 4.5]	0.76

	3000-10000	25.6	[18.8, 32.5]	34.3	[27.2, 41.4]	
	10001-20000	32.1	[24.7, 39.4]	26.9	[20.3, 33.5]	
	20001-30000	19.2	[13.0, 25.4]	17.1	[11.5, 22.8]	
	30001-40000	5.1	[1.6, 8.6]	4.6	[1.5, 7.7]	
	40001-50000	5.1	[1.6, 8.6]	5.7	[2.3, 9.2]	
	>50000	9.6	[5.0, 14.30]	9.1	[4.9, 13.4]	
Health Insurance	Yes	15.4	[9.7, 21.1]	19.4	[13.5, 25.3]	0.335
	No	84.6	[78.9, 90.3]	80.6	[74.7, 86.5]	
Site Location						
Madras Diabetes Research Foundation (Chennai)		37.8	[30.2, 45.5]	36.0	[28.9, 43.1]	0.902
All India Institute for Medical Sciences (Delhi)		22.4	[15.9, 29.0]	25.7	[19.2, 32.2]	
Endocrine Diabetes Clinic (Visakhapatnam)		17.9	[11.9, 24.0]	18.3	[12.5, 24.0]	
Diacon Hospital (Bengaluru)		21.8	[15.3, 28.3]	20.0	[14.0, 26.0]	
Clinical Characteristics, N (%) or mean (SD)						
Duration of Diabetes		8.9 (7.0)	[7.7, 10.0]	9.6 (7.3)	[8.5, 10.7]	0.6208
How diagnosed with diabetes	Testing after symptoms emerged or at medical visit for symptoms of other diseases	25.6	[18.8, 32.5]	24.0	[17.6, 30.4]	0.73
	Revealed at routine check-up (no symptoms present)	74.3	[67.5, 81.2]	76.0	[69.6, 82.4]	
Neuropathy (hands and feet)	Yes	18.6	[12.5, 24.7]	14.9	[9.6, 20.2]	0.363
	No	81.4	[75.3, 87.5]	85.1	[79.8, 90.4]	
Insulin	Yes	34.0	[26.5, 41.4]	34.3	[27.2, 41.3]	0.953
	No	66.0	[58.6, 73.5]	65.7	[58.6, 72.8]	

OHA	Yes	93.0	[88.9, 97.0]	92.0	[88.0, 96.0]	0.745
	No	7.1	[3.0, 11.1]	8.0	[4.0, 12.0]	
Blood Pressure Medication	Yes	52.6	[44.7, 60.4]	49.1	[42.0, 56.6]	0.535
	No	47.4	[39.6, 55.3]	50.9	[43.4, 58.3]	
Antidepressant	Yes	6.4	[2.5, 10.3]	3.4	[0.7, 6.1]	0.208
	No	93.6	[89.7, 97.4]	96.6	[96.6, 99.3]	
Smokes Tobacco	Never	92.3	[88.1, 96.5]	94.9	[91.6, 98.1]	0.632
	Quit	3.2	[0.4, 6.0]	2.2	[0.1, 4.5]	
	Current	4.5	[1.2, 7.8]	2.9	[0.4, 5.3]	
Cardiometabolic and Depression Characteristics, N(%) or mean (SD)						
BMI, kg/m^(2)		27.1 (5.3)	[26.2, 27.9]	27.1 (4.7)	[26.4, 27.8]	0.1125
Weist circumference (cm)		95.6 (12.2)	[93.7, 97.5]	94.3 (13.1)	[92.4, 96.3]	0.3550
FBG, mg/dL		180.6 (68.5)	[169.9, 191.4]	181.5 (75.0)	[170.4, 192.7]	0.2418
Hemoglobin A1C, %		9.3 (1.9)	[9.0, 9.6]	9.0 (1.8)	[8.8, 9.3]	0.4036
Total Cholesterol, mg/dL		176.2 (46.9)	[168.8, 183.6]	179.5 (42.1)	[173.2, 185.7]	0.1649
LDL, mg/dL		101.7 (38.3)	[95.7, 107.8]	104.3 (37.8)	[98.6, 110.0]	0.8896
HDL, mg/dL		40.7 (9.7)	[39.2, 42.2]	44.0 (13.0)	[42.0, 45.9]	0.0003
Triglycerides, mg/dL		167.4 (95.4)	[152.4, 182.5]	158.8 (78.6)	[147.2, 170.5]	0.0129
SBP, mmHg		132.0 (17.8)	[129.5, 134.5]	131.5 (17.8)	[128.9, 134.2]	0.2003
DBP, mmHg		80.4 (11.2)	[78.6, 82.1]	80.0 (10.0)	[78.2, 81.2]	0.1703
Weight (kg)		69.1 (13.7)	[66.9, 71.2]	66.7 (12.3)	[64.9, 68.6]	0.1561
SCL-20 Score		25.5 (10.5)	[23.8, 27.2]	27.4 (10.9)	[25.8, 29.0]	0.6147
PHQ-9 Score		13.0 (2.5)	[12.6, 13.4]	13.6 (2.6)	[13.2, 14.0]	0.6598
History of CVD	Yes	3.2	[0.4, 6.0]	4.0	[1.1, 6.9]	0.7

	No	96.8	[94.0, 100.0]	96.0	[93.1, 98.9]	

Table 2. Adjusted Differences in Means of Key Treatment Targets Between Collaborative Care and Usual Care at 36 Months^

Outcome			Risk Difference at 36 months (95% CI)		Risk Ratios at 36 months (95% CI)	
	Collaborative Care Group (%)	Usual Care Group (%)	36 Months	p-value	36 Months	p-value
Primary Outcome*	62.1%	57.8%	4.3 [-6.2-1.5]	0.4229	1.07 [0.90, 1.27]	0.4378
Secondary Outcomes - Single measures						
≥50% improvement in SCL-20 score	72.4%	69.7%	2.3 [-7.2-11.7]	0.6370	1.03 [0.90-1.17]	0.6687
≥0.5-percentage point reduction in HbA1c	52.9%	42.1%	10.0 [-0.3-2.1]	0.0579	1.26 [1.00-1.56]	0.0413
≥5-mm Hg reduction in SBP	44.2%	47.4%	-3.0 [-13.7-7.7]	0.5863	0.94 [0.75-1.19]	0.6062
≥10-mg/dL reduction in LDL	32.7%	26.3%	4.0 [-6.7-14.7]	0.4615	1.09 [0.85-1.40]	0.5049
HbA1c <7%	17.6%	13.5%	3.3 [-4.8-11.4]	0.4192	1.34 [0.80-2.23]	0.2611
SBP <130 mm Hg	46.1%	51.4%	-5.2 [-1.6-5.6]	0.3480	0.90 [0.72-1.13]	0.3736
LDL <100 mg/dL (<70 mg/dL with history of CVD)	45.1%	41.4%	4.0 [-6.0-14.7]	0.4615	1.09 [0.85-1.40]	0.5049
Secondary Outcomes - Composite measures						
≥0.5-percentage point reduction in HbA1c or HbA1c <7%	54.2%	45.0%	8.9 [-1.9-19.1]	0.1065	1.21 [0.98-1.49]	0.0804
≥5-mm Hg reduction in SBP or SBP <130 mm Hg	57.1%	63.4%	-6.1 [-16.6-4.4]	0.2573	0.90 [0.76-1.07]	0.2446
≥10-mg/dL reduction in LDL or LDL-C <100 mg/dL (<70 with history of CVD)	45.1%	41.4%	4.0 [-6.7-14.7]	0.4615	1.09 [0.85-1.40]	0.5049
HbA1c <7%, SBP <130 mm Hg, and LDL-C <100 mg/dL (<70 with history of CVD)	1.3%	4.1%	-2.5 [-10.9-6.0]	0.5669	0.36 [0.07-1.59]	0.1681

Secondary outcomes – continuous measures			Mean Difference at 36 Months (95% CI)	p-value		
SCL-20 mean, score	7.9 (6.4)	8.8 (6.5)	-0.9 [-2.3-0.5]	0.2786		
PHQ-9 mean, score	4.8 (3.6)	5.1 (3.6)	-0.4 [-1.1-0.4]	0.0563		
HbA1c, mean, %	9.1 (5.9)	8.9 (1.9)	0.1 [-0.8-1.1]	0.3993		
SBP, mean, mm Hg	129.1 (14.3)	129.5 (17.5)	-0.5 [-0.4-3.0]	0.8434		
LDL, mean, mg/dL	108.6 (42.2)	110.8 (44.5)	-2.3 [-11.7-7.2]	0.5369		

^At 36 months, out of N = 331 patients, there were 5 missing for the primary outcome; 9 missing for SCL-20 outcomes; 7 missing for HbA1c outcomes; 2 missing for SBP outcomes; and 3 missing for HbA1c outcomes

**≥50% Improvement in SCL-20 and ≥0.5-percentage point HbA1c reduction, ≥5-mm Hg SBP reduction, or ≥10-mg/dL LDL-C reduction*

Table 3: Primary Outcome at 36 Months by Socioeconomic and Clinical Characteristics Between Collaborative Care vs. Usual Care Groups

	Risk Difference (95% CI)	p-value	Risk Ratio (95% CI)	p-value
Age (years)				
</= 49	2.9 [-13.9-19.8]	0.4810	1.02 [0.79-1.32]	0.3970
> 50	4.8 [-8.4-18.0]		1.09 [0.87-1.37]	
Sex				
Male	-0.9 [-18.1-16.2]	0.4777	0.99 [0.75-1.30]	0.5240
Female	6.9 [-6.4-20.1]		1.11 [0.89-1.39]	
Level of Education				
Less than primary	10.6 [-15.7-37.0]	0.0659	1.12 [0.65-1.93]	0.0900
Primary or Secondary	5.6 [-6.6-17.8]		1.08 [0.90-1.30]	
Post-Secondary	-16.3 [-47.4-14.8]		0.73 [0.38-1.39]	
Household Income (INR)				
< 10000	18.3 [0.6-35.9]	0.6405	1.31 [1.00-1.72]	0.7070
>/= 10000	-1.4 [-14.4-11.5]		0.98 [0.78-1.22]	
Duration of diabetes (years)				
</= 8	11.7 [-2.6-25.9]	0.2540	1.21 [0.96-1.53]	0.3490
> 8	-3.9 [-19.6-11.7]		0.93 [0.71-1.21]	
Site				
MDRF (private)	-0.9 [-17.6-15.7]	0.0117	0.99 [0.77-1.26]	0.0830
AIIMS (public)	6.9 [-14.7-28.5]		1.12 [0.79-1.59]	
EDC (private)	19.5 [-5.2-44.1]		1.40 [0.90-2.19]	
DIACON (private)	-1.6 [-25.1-21.9]		0.97 [0.57-1.63]	

Figure 1: INDEPENDENT Participant Eligibility and Collaborative Care Component

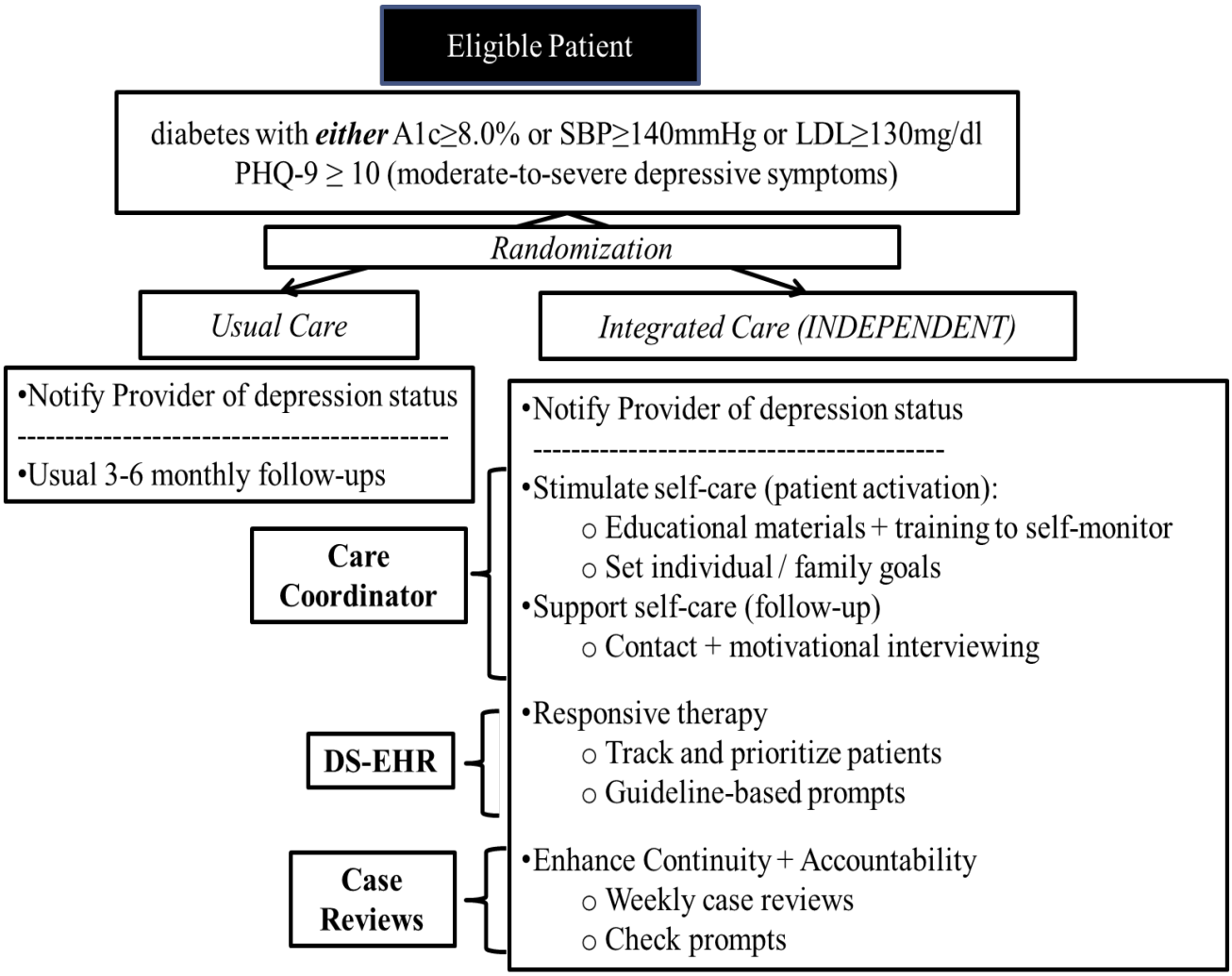
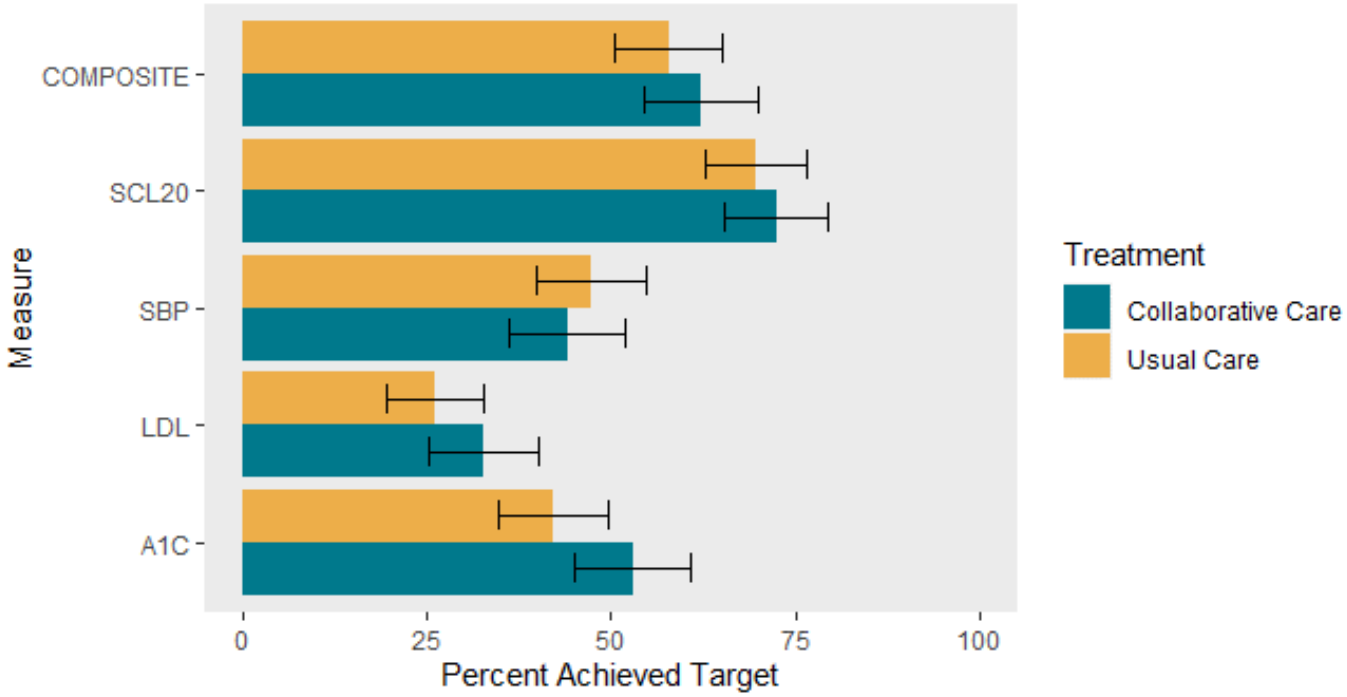
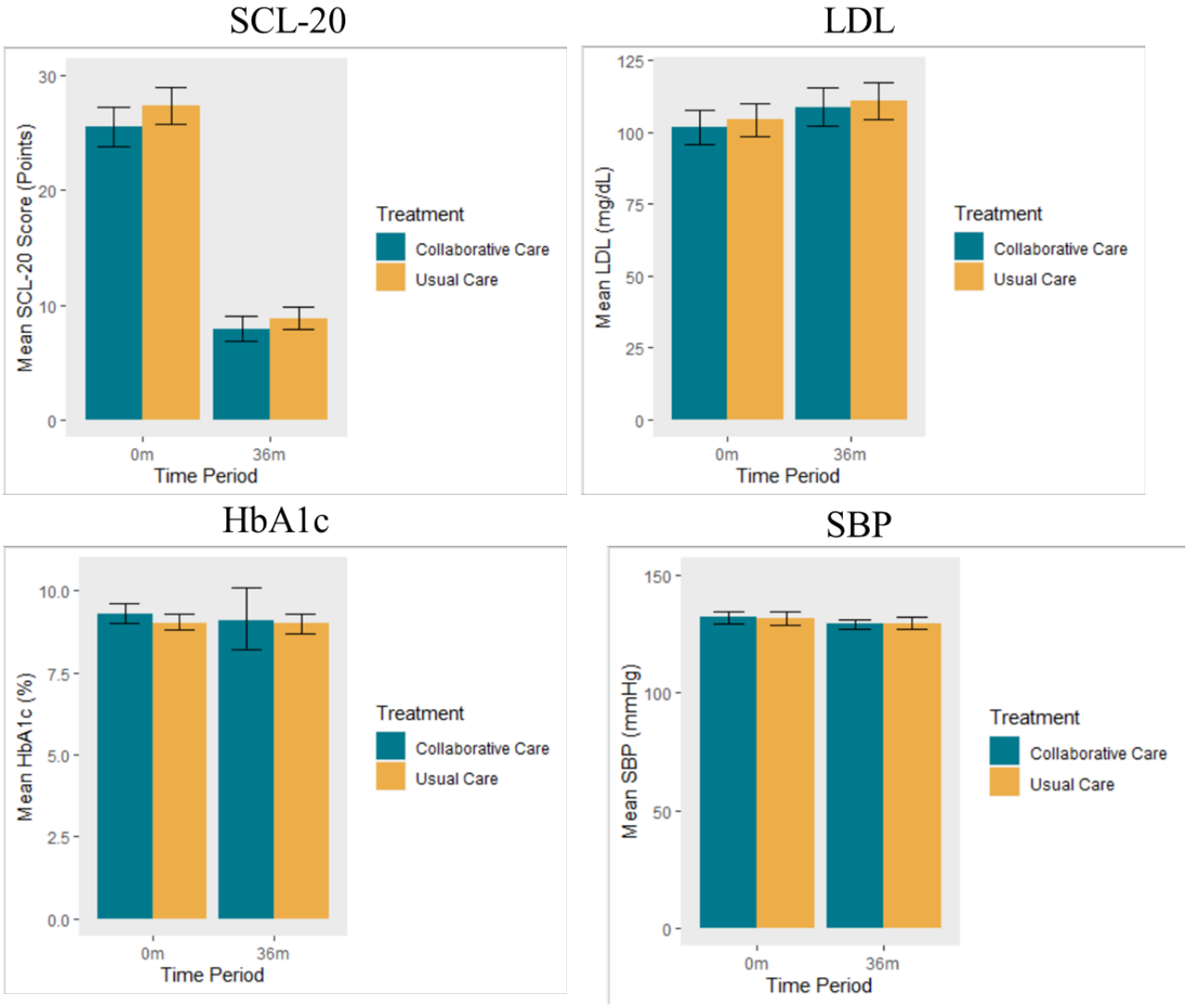


Figure 2: Proportion of Participants Achieving Treatment Targets by Arm at 36 Month Follow-Up



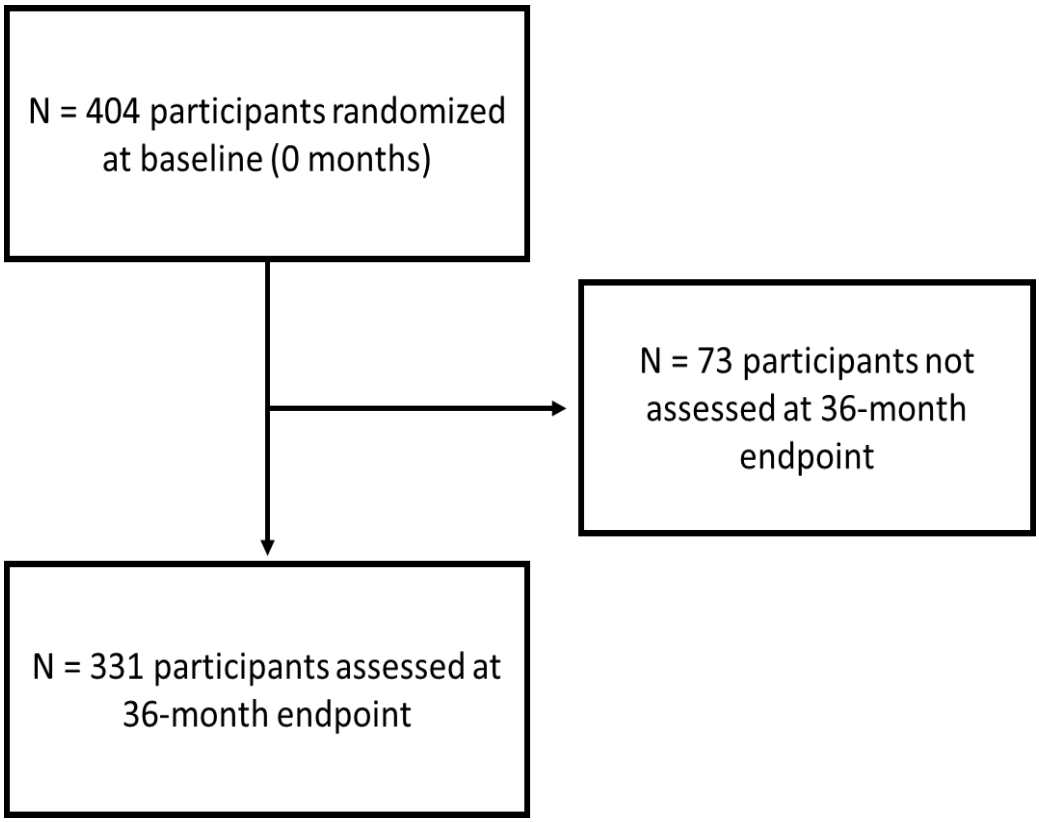
^Abbreviations: COMPOSITE = patients who had at least 50% improvement in SCL-20 scores and at least one of the following: at least 0.5-percentage point (ppt) reduction in HbA1c, at least 5-mm Hg reduction in SBP, or at least 10-mg/dL reduction in LDL cholesterol at 36 months; SCL20 = at least 50% improvement in SCL-20 score at 36 months; SBP = at least 5-mm Hg reduction in SBP at 36 months; LDL = at least 10-mg/dL reduction in LDL cholesterol at 36 months; A1C = at least 0.5-percentage point (ppt) reduction in HbA1c at 36 month

Figure 3. Mean Outcomes for Depression and Cardiometabolic Indicators at Baseline and 36 Months



Supplemental Material

Supplemental Figure 1: Participants Lost to Follow-Up from Baseline to 36 Months



Supplemental Table 1. Differences Between Participants Not Assessed at 36 months and Completing Participants (N = 404)

		Completing Participants (N =331)	**95% CI**	**Participants Not Assessed at 36 months (N = 73)**	**95% CI**	**p-value**
Demographic Characteristics, N(%) or mean(SD)						
Sex	Female	62.5	[57.3, 67.8]	43.8	[32.4, 55.3]	0.0034
	Male	56.2	[44.7, 67.6]	37.5	[32.2, 42.7]	
Age, mean (SD)		52.6 (8.4)	[51.7, 53.5]	53.5 (9.3)	[51.7, 533.5]	0.2836
Marital Status	Married	84.3	[80.4, 88.2]	90.4	[83.6, 97.2]	N/A
	Single	1.2	[0.0, 2.4]	0.0	--	
	Divorced/Separated	1.2	[0.0, 2.4]	4.1	[0.0, 8.7]	
	Widowed	13.3	[9.6, 17.0]	5.5	[0.2, 10.7]	
Education	Post-secondary	19.0	[14.8, 23.3]	38.4	[27.2, 49.6]	0.0004
	Secondary or primary school	69.2	[64.2, 74.2]	58.9	[47.6, 70.2]	
	Less than primary school or unsure	11.8	[8.3, 15.3]	2.7	[0.0, 6.5]	
Occupation	Employed, training	34.1	[29.0, 39.3]	47.9	[36.4, 59.4]	0.0044
	Employed, no training	4.8	[2.5, 7.2]	1.4	[0.0, 4.0]	
	Housewife	53.8	[48.4, 59.2]	34.2	[23.3, 45.2]	
	Retired	6.3	[3.7, 9.0]	13.7	[5.8, 21.6]	
	Unemployed	0.9	[0.0, 1.9]	2.7	[0.0, 6.5]	

Household Income, INR	< 3000	2.7	[1.0, 4.5]	1.4	[0.0, 4.0]	0.0424
	3000-10000	30.2	[25.2, 35.2]	15.1	[6.8, 23.3]	
	10001-20000	29.3	[24.4, 34.2]	27.4	[17.1, 37.7]	
	20001-30000	18.2	[14.0, 22.3]	20.5	[11.2, 29.9]	
	30001-40000	4.8	[2.5, 7.2]	11.0	[3.8, 18.2]	
	40001-50000	5.4	[3.0, 7.9]	8.2	[1.9, 14.5]	
	>50000	9.4	[6.2, 12.5]	16.4	[7.9, 25.0]	
Health Insurance	Yes	17.5	[13.4, 21.6]	17.8	[9.0, 26.6]	0.9538
	No	82.5	[73.4, 91.0]	82.2	[73.4, 91.0]	
Site Location						
Madras Diabetes Research Foundation (Chennai)		36.9	[31.6, 42.1]	45.2	[33.7, 56.7]	0.0016
All India Institute for Medical Sciences (Delhi)		24.2	[19.5, 28.8]	13.7	[5.8, 21.6]	
Endocrine Diabetes Clinic (Visakhapatnam)		18.1	[14.0, 22.3]	32.9	[22.1, 43.7]	
Diacon Hospital (Bengaluru)		20.8	[16.5, 25.2]	8.2	[1.9, 14.5]	
Clinical Characteristics, N (%) or mean (SD)						
Duration of Diabetes						
How diagnosed with diabetes	Testing after symptoms emerged or at medical visit for symptoms of other diseases	24.8	[20.1, 29.4]	38.4	[27.2, 49.6]	0.0188
	Revealed at routine check-up (no symptoms present)	75.2	[70.6, 79.9]	61.6	[50.4, 72.8]	

Neuropathy (hands and feet)	Yes	0.3	[0.0, 0.9]	0.0	--	N/A
	No	99.7	[99.1, 100.0]	100	--	
Insulin	Yes	34.1	[29.0, 39.3]	32.9	[22.1, 43.7]	0.8367
	No	65.9	[60.7, 71.0]	67.1	[56.3, 77.9]	
OHA	Yes	92.4	[89.6, 95.3]	94.5	[89.3, 99.8]	0.5348
	No	7.6	[4.7, 10.4]	5.5	[0.2, 10.7]	
Blood Pressure Medication	Yes	46.4	[45.3, 56.2]	43.8	[32.4, 55.3]	0.2851
	No	45.2	[43.8, 54.7]	56.2	[44.7, 67.6]	
Antidepressant	Yes	4.8	[2.5, 7.2]	4.1	[0.0, 8.7]	0.7915
	No	95.2	[92.8, 97.5]	95.9	[91.3, 100.0]	
Cardiometabolic and Depression Characteristics, N(%) or mean (SD)						
BMI, kg/m^(2)		27.1 (5.0)	[26.5, 27.6]	25.2 (5.8)	[23.9, 26.6]	0.1250
Weist circumference (cm)		94.9 (12.7)	[93.5, 96.3]	94.0 (10.8)	[91.5, 96.6]	0.1088
FBG, mg/dL		181.0 (71.9)	[173.3, 188.9]	186.1 (74.6)	[168.7, 203.5]	0.6663
Hemoglobin A1C, %		9.1 (1.9)	[8.9, 9.4]	9.1 (2.2)	[8.6, 9.6]	0.0605
Total Cholesterol, mg/dL		177.9 (44.4)	[173.1, 182.7]	155.8 (38.2)	[146.9, 164.7]	0.1233
LDL, mg/dL		103.1 (38.0)	[99.0, 107.2]	91.0 (37.1)	[82.4, 99.7]	0.8155
HDL, mg/dL		42.2 (11.7)	[41.2, 43.7]	38.6 (10.4)	[36.2, 41.1]	0.2236
Triglycerides, mg/dL		162.9 (86.9)	[153.5, 172.3]	151.1 (64.0)	[136.2, 166.1]	0.0022
SBP, mmHg		131.8 (17.0)	[129.9, 133.6]	136.9 (13.1)	[133.8, 139.9]	0.0089
DBP, mmHg		80.0 (10.6)	[78.9, 81.2]	82.7 (9.2)	[80.6, 84.9]	0.1529
Weight (kg)		67.8 (13.0)	[66.4, 69.3]	67.2 (11.9)	[64.4, 70.0]	0.3535
SCL-20 Score		26.5 (10.7)	[25.3, 27.7]	27.8 (8.1)	[25.9, 29.7]	0.0047

PHQ-9 Score		13.3 (2.5)	[13.0, 13.6]	13.0 (2.3)	[12.4, 13.5]	0.4073
History of CVD	Yes	3.6	[1.6, 5.6]	9.6	[2.8, 16.4]	0.0299
	No	83.0	[94.4, 98.4]	96.4	[94.4, 98.4]	

Supplement Table 2. Common Effect Outcome at 12-, 24-, and 36-Month Follow-Up.

	Collaborative Care		**Usual Care**	
	Common Effect	95% CI	Common Effect	95% CI
12 months -Post-intervention	-0.2250	(-0.3303, -0.1197)	0.00 (reference)	n/a
24 months -Post-intervention	-0.1118	(-0.2254 0.0018)	0.00 (reference)	n/a
36 months-Post-intervention	0.0434	(-0.0880, 0.1749)	0.00 (reference)	n/a

Chapter III: Summary, Implications, & Future Directions

Summary

T2D and depression is becoming increasingly prevalent in low-and middle-income countries. The bi-directional influence of T2D and depression on the development and management of each condition well known and an area for concern. Additionally, management for these conditions is complex and is constrained by the lack of mental health specialists (Garg et al., 2019). Interventions to address these comorbid diseases with resources constraints is not well-researched; the World Health Organization has even called for the urgent need to address mental disorders and other chronic conditions simultaneously (*Integrating the Response to Mental Disorders and Other Chronic Diseases in Health Care Systems*, 2014; Alzoubi et al., 2018; Patel & Chatterji, 2015).

Of the evidence we do have regarding models of care to address these diseases, almost all are within the context of high-resource countries. Furthermore, most studies examining interventions to address comorbid T2D and depression only followed up with patients in the short-term (Ghaeli et al., 2004; P. J. Lustman et al., 1997; Patrick J. Lustman et al., 2006). Additionally, all of these studies took place in the Global North (and mostly in the U.S.), despite the concentrated burden of chronic conditions in the Global South (*Non Communicable Diseases*, n.d.). These gaps in our understanding of the effectiveness of interventions to treat comorbid T2D and depression in the long-term in India and other LMICs hamper our ability to address these conditions in the global population.

The results from this study show that it is difficult to sustain changes that develop from a short-term intervention. The intervention effects of the collaborative care model were active for

12 months – this amount of time is enough to form long-term habits for lasting change and so the regression back to baseline may suggest that systemic barriers may be inhibiting long-term change (Gardner et al., 2012).

The difficulty in sustaining collaborative care models to affect meaningful and lasting changes in cardiometabolic indices for a patient additionally supports the case for primary prevention of T2D, hypertension, and hypercholesteremia. Beyond the healthcare system, a lack of green spaces, inadequate intake of fresh fruits and vegetables (due to price), and fragmented population-based chronic disease surveillance systems all contribute to systemic barriers in the ability to maintain cardiometabolic health (Choudhury et al., 2020; Pati et al., 2020). Therefore, systemic solutions involving policy creation for healthier living, pedestrian-optimized infrastructure prioritization, and healthcare resource allocation are necessary.

Short-and-long term T2D prevention programs have shown lasting and effective change, especially when these programs are focused on lifestyle and behavior change and are integrated into already-existing systems (*National Diabetes Prevention Program | Diabetes | CDC*, 2019; Porterfield et al., 2010; Ramachandran et al., 2006). Implementation of such programs are more difficult in resource-constrained settings with fragmented health care – like India – and so further investment and research is needed to understand how to best operationalize chronic disease prevention programs in these settings.

Implications & Future Directions

Depressive symptoms were lowered during the intervention period and remained low in the post-intervention follow-up. By 36 months, we observed marked improvement in depressive symptoms since baseline in both the collaborative care group and usual care group. In contrast, cardiometabolic symptoms reverted to baseline levels at the 36-month endpoint in both the

intervention and control groups. The difference in sustainability of outcomes in this trial warrants deeper investigation into the reasons for this differential improvement, and possibly larger trials in similar settings (e.g., fragmented medical care, low number of psychiatrists) in which differences in the effects of individuals intervention components can be detected.

Systemic changes to policies, infrastructure, healthcare systems, and health insurance provision that enable continued offering of the collaborative care model to patients with poorly controlled diabetes should be explored.

Additionally, the difficulty in sustaining metabolic control among individuals with diabetes reinforces the call for primordial prevention. Prevention strategies such as the Indian Diabetes Prevention Programme (IDPP), should be scaled up across urban areas of India (Ramachandran et al., 2006). Prevention of T2D has been proven to affect lasting change for years and even a decade (Diabetes Prevention Program Research Group et al., 2009). Furthermore, addressing the social and political determinants of health may provide the most sustained population-level benefits for cardiometabolic disease. Policies that enable access to healthy food, infrastructure to promote safety and consistent usage, and national health insurance schemes should be explored as options in efforts to decreasing the burden of chronic diseases and mental health disorders in India.

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