Original Article

The Impact of a Collaborative Care Model on Health Trajectories among Patients with Co–Morbid Depression and Diabetes: The INDEPENDENT Study

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Abstract

Context: Collaborative care models for depression have been successful in a variety of settings, but their success may differ by patient engagement. We conducted a post-hoc analysis of the INDEPENDENT trial to investigate the role of differential engagement of participants on health outcomes over 3 years. **Settings and Design:** INDEPENDENT study was a parallel, single-blinded, randomised clinical trial conducted at four socio-economically diverse clinics in India. Participants were randomised to receive either active collaborative care or usual care for 12 months and followed up for 24 months. **Method:** We grouped intervention participants by engagement, defined as moderate (≤7 visits) or high, (8 or more visits) and compared them with usual care participants. Improvements in composite measure (depressive symptoms and at least one of three cardio-metabolic) were the primary outcome. **Statistical Analysis:** Mean levels of depression and cardio-metabolic measures were analysed over time using computer package IBM SPSS Statistics 25. **Results:** The composite outcome was sustained the highest in the moderate engagers [27.5%, 95% confidence interval (CI): 19.5, 36.7] and the lowest in high engagers (15.8%, 95% CI: 8.1, 26.8). This pattern was observed for individual parameters – depressive symptoms and glycosylated haemoglobin. Progressive reductions in mean depressive symptom scores were observed for moderate engagers and usual care group from baseline to 36 months. However, in high engagers of collaborative care, mean depressive symptoms were higher at 36 months compared to 12 months. **Conclusion:** Sustained benefits of collaborative care were larger in participants with moderate engagement compared with high engagement, although a majority of participants relapsed on one or more outcome measures by 36 months. High engagers of collaborative care for co-morbid depression and diabetes may need light touch interventions for longer periods to maintain health and reduce depressive symptoms.

Keywords: Cardio-metabolic health, collaborative care, co-morbidity, depression, diabetes, trajectories

Introduction

Diabetes is one of the fastest growing health challenges of the 21st century. The number of adults living with diabetes has more than tripled over the past 20 years.[1] The current estimate is 537 million living with diabetes worldwide.[2] It is a chronic metabolic disorder characterised by elevated levels of blood glucose, which leads to complications of the eyes, kidneys, heart, blood vessels, and nerves.[3]

Diabetes commonly coexists with depression.[4] Depression is a common illness affecting more than 300 million people worldwide.[5] Chronic and severe depression can have considerable ill effects on health. Depression is a leading cause

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of disability around the world and contributes greatly to the global burden of disease.[5] The effects of depression can be long-lasting or recurrent and can dramatically affect a person's ability to function and live a satisfying life. Public awareness and public health resources to address mental health are limited in low- and middle-income countries (LMICs).[6]

The majority of research on the relationship between diabetes and depression comes from high-income nations; however, the fact is that over 80% of individuals with diabetes live in low- and middle-income countries[2] and people with diabetes are 2–3 times more likely to have depression than people without diabetes.[7] A systematic review estimated the global prevalence of depression among people with T2DM at 28%, with Asia having the highest rate of depression at 32%.[8] Because of the bidirectional influence of diabetes and depression on one another, persons with both depression and diabetes experience poor health outcomes such as reduced glycaemic control, increased complications, and poor self-management along with greater health care use, compared to those with either of the conditions alone.[9–16] Only 25–50% of individuals with diabetes and depression receive a diagnosis and treatment for it.[17] Models of care that address both diabetes and depression simultaneously have thus been proposed to meet the needs of patients. Collaborative care is based on four principles: a multi-professional approach to patient care, structured management plan, scheduled patient follow-ups, and enhanced inter-professional communication.[18,19] Past research has demonstrated that collaborative care has greater improvements on depressive symptoms when compared to usual care.[20,21]

The Integrating DEPrEssioN and Diabetes treatmENT (INDEPENDENT) study was a trial to investigate the effect of integrating a collaborative care approach for depression to clinical practice at diabetes clinics. The study was implemented to test whether this integrated and scalable model of care was effective to improve both depressive symptoms and multiple risk factors control in patients in India.[22] In the primary analysis of the INDEPENDENT study, a significantly greater percentage of patients in the intervention group versus the usual care group achieved the primary composite outcome, that is, reduction in depressive symptoms combined with improvement in at least one cardio-metabolic health parameter (71.6% vs 57.4).[23] Among collaborative care participants, however, there was substantial heterogeneity in engagement with intervention activities (e.g., visits with the health care team). Whether this differential engagement played a role in intervention outcomes and how intervention engagement impacted sustainment of outcomes after the conclusion of the primary evaluation period remain unclear.

The purpose of this study is to conduct post-hoc analysis of the INDEPENDENT trial to investigate differential engagement of participants in collaborative care and the role of the same on participant outcomes over 3 years post-randomisation.

Methods

The INDEPENDENT trial design and participants

INDEPENDENT study was a parallel, single-blinded, randomised clinical trial conducted at four socio-economically diverse clinics (private clinics in Chennai, Bangalore, and Visakhapatnam and a large public hospital in Delhi) in India.

Patients were eligible for inclusion if they were aged at least 35 years and had type 2 diabetes, mild to moderate depressive symptoms [9-item patient health questionnaire (PHQ-9) score ≥10], and at least one poorly controlled cardio-metabolic parameter [glycosylated haemoglobin (HbA1c) 8%, systolic blood pressure (SBP) ≥140 mmHg, or low-density lipoprotein (LDL-c) cholesterol ≥130 mg/dL]. Patients with alcohol or substance use disorders, bipolar or psychotic disorders, type 1 diabetes, kidney failure, or cardio-vascular disease (CVD) events in the past 12 months (myocardial infarction, unstable angina, or stroke), severe depressive symptoms, and suicidal ideation [a "3" is reported for the PHQ-9 questionnaire suicide item (item #9)] were excluded.

A total of 404 participants with diabetes and depressive symptoms were randomised from the four study sites; a total of 196 participants were randomised to the intervention arm (collaborative care), and 208 participants were randomised to usual care.

Participants randomised to the intervention group received collaborative care for 12 months. The remaining 24 months involved passive follow-up without intervention to determine if 12 months of exposure to collaborative care had a sustained effect. Usual care participants received clinical care based on local standards for 36 months.

Collaborative care

The details of collaborative care provided are detailed in earlier publications.[22,23] However, a brief description is provided below.

The collaborative care was designed to include interventions that were culturally relevant using inputs from the INDEPENDENT study's formative research. It included the following components: 1) to engage families in the treatment process, 2) to provide clear/simple written information, 3) use of non-jargon verbal explanations, and 4) coaching to help patients cope with stigma, which would add value when incorporated into the intervention.[24]

The study team integrated a decision support electronic health record (DS-EHR) system into clinic workflows to assist the physicians in their clinical decision-making and the initiation and/or timely modification of pharmacotherapies for depression, glucose, blood pressure, and lipid management.

The intervention consisted of patient-centred methods to overcome barriers and facilitate patient-level (e.g., self-care), clinician-level (e.g., measurement-based treatment to target), and system-level (e.g., monitoring patient panels, outreach to

patients with the most poorly controlled health parameters) improvements.

Each site had a team comprising a care coordinator [non-physician, allied health care professional with no prior training in mental health management (e.g., dietitians, health counsellors)] and two consulting specialists (qualified psychiatrist and diabetologist). They supplemented the diabetes physicians via offline case review meetings twice a month.

Usual care

The participants who were assigned to the usual care continued to see their regular diabetic physician for diabetes management according to standard operating procedures of each centre. Participants in usual care generally visited the centre once in 3 months.

Study visits and intervention visits

All participants were assessed for study outcomes at baseline and five study visits (at 6, 12, 18, 24, and 36 months). In addition, data on health parameters were collected at all intervention visits (phone visits and clinic visits). The DS-EHR was a primary tool to call study participants for intervention visits. Intervention visits were planned based on the participants' depressive symptoms, glycaemic values, blood pressure, and other biochemical parameters reflecting inadequate treatment or poor disease control. Two weeks was the earliest a participant might be asked to come in for an intervention visit. In this study, we examined data from the intervention visits along with data from the study visits.

Institutional ethics committees at each participating site and the coordinating centres approved the study protocol. The eligible patients gave written informed consent prior to enrolment. The detailed trial protocol has been described and was published separately prior to the study completion.[22]

Study outcomes

In the current study, we examined depressive symptom (PHQ-9) outcomes along with four cardio-metabolic parameters related to diabetes management: fasting plasma glucoses (FPG), HbA1c, SBP, and LDL-c, along with body weight in kilograms (kg). The four cardio-metabolic parameters assessed in this study are the same parameters that determined inclusion of participants in the study. Assessors used PHQ-9 score for measuring depressive symptom severity. They also used standardised protocols for measuring blood pressure (three readings spaced 5 minutes apart in resting position using Omron T9P instruments) and collected blood samples for measurements of FPG, HbA1c, and LDL cholesterol, analysed by local laboratories which were enrolled in an external quality assurance scheme. Body weight was measured using standard procedures and calibrated digital weighing scales.

Data from intervention visits and study visits were used to assess the trajectories of depressive symptoms and cardio-metabolic parameters. The participants at 12 months, 24 months, and 36 months, who had at least a 50% reduction in PHQ-9 scores, a reduction of at least 0.5 percentage points in HbA1c or 5 mmHg in SBP, or 10 mg/dL in LDL-c, were studied. The composite study outcome was defined as ≥50% reductions in PHQ–9 scores and / either ≥0.5 percentage point (ppt) HbA1c reduction, ≥5mmHg SBP reduction, or ≥10mg/dL LDL–c reduction.

Intervention engagement

To study the long-term response to the multi-component collaborative care, the participants' total number of visits was accounted for post-hoc and the median of visits was calculated (median = 8). The participants of the collaborative care were further categorised as moderate engagers of collaborative care (moderate engagers) when they had seven intervention visits or fewer and high engagers of collaborative care (high engagers) when they had eight or more intervention visits.

Response types

We identified groups of treatment responses over 36 months of follow-up after randomisation. Participants were categorised as 'responder' when they achieved the outcome at the end of 12 months. Of responders at 12 months, we further classified participants as 'sustained responder' when they sustained the improvement at 24 and 36 months and 'non-sustained responder' when they responded at 12 months but did not sustain the improvement at 24 or 36 months.

There were some participants who did not achieve study outcomes at 12 months; however, they achieved study outcomes thereafter. Those outcomes are not reported here.

Statistical analysis

The computer package IBM SPSS Statistics 25 (IBM Corporation, Armonk, New York, United States) was used for statistical analysis. We described the sociodemographic characteristics and biochemical parameters of the study population by reporting mean ± standard deviation or proportions. We also compared baseline characteristics between the full intervention and usual care groups as well as the moderate engagers and high engagers groups within the intervention group.

To compare baseline characteristics across the study groups, Student's t tests were used for continuous variables, whereas Pearson's Chi-square ($\chi 2$) test or Fisher's exact test was used to test differences in categorical variables. A two-tailed p value<0.05 was considered significant.

The percentage (and 95% confidence interval, CI) achieving depressive symptom and cardio-metabolic outcomes were calculated and presented at each time point. We also examined the trajectories of FPG, HbA1c, body weight, and PHQ-9 scores of participants by calculating the mean during the intervention period and the follow-up across three arms – the usual care, moderate engagers, and high engagers.

Ethical Clearance Statement

The study was approved by Emory University Institutional Review Board vide IRB00064913 on 10th June 2013 at Emory University; Institutional Ethics Committee of Madras

Diabetes Research Foundation vide MDRF/NCT/29-04/2013 on 01st May 2013 at Madras Diabetes Research Foundation; Institutional Ethics Committee – All India Institute of Medical Sciences vide IEC/30052013 on 31st May 2013 at All India Institute of Medical Sciences; Institutional Ethics Committee of Endocrine and Diabetes Center vide IEC/30052013 on 31st May 2013 at Endocrine and Diabetes Centre and DIACON Ethics Committee vide IEC/30052015 on 2nd May 2015 at DIACON (Diabetes Care and Research Centre).

Results

Of the 404 participants randomised in this study, 196 were randomised to the intervention arm and 208 to the usual care. A total of 394 participants (intervention arm: 192; usual care: 202) completed the 12-month follow-up, 378 participants (intervention arm: 185; usual care: 193) completed the 24 months follow-up, and 331 participants (intervention arm: 164, usual care: 167) completed the 36 months follow-up. The intervention participants were categorised post-hoc according to intervention exposure, of which 129 were moderate engagers and 67 participants were high engagers.

At baseline, participants in the intervention arm and usual care groups had similar demographic and health characteristics [Table 1]. However, participants who were classified as moderate engagers were more likely to have longer duration of diabetes with microvascular complications, insulin use, higher HbA1c values, and lower SBP values at baseline when compared to high engagers.

Table 2 shows the responders at the end of the intervention phase followed by sustained responders and non-sustained responders at 24 and 36 months. At 12 months, the composite study outcome (i.e., 50% improvement in PHQ-9 along with one of the following parameters: ≥0.5 ppt HbA1c reduction or ≥5 mmHg SBP reduction or ≥10 mg/dL LDL-c reduction) was seen most in the high engagers (83.6%, 95% CI: 73.4, 91.0) followed by moderate engagers (60.0%, 95% CI: 51.3, 68.3) and then by the usual care group (45.4%, 95% CI: 38.8, 52.4). There was a significant difference between the responders and non-responders at 12 months for composite outcome and depressive symptoms.

At 24 months, the composite study outcome was sustained most in the high engagers (45.5%, 95% CI: 33.9, 57.4) followed by the moderate engagers (44.5%, 95% CI: 35.8, 53.5) and then the usual care group (23.6%, 95% CI: 18.0, 29.9). There was a significant difference between the three groups at 24 months.

When individual parameters were studied, with respect to depressive symptoms, the high engagers (57.6%, 95% CI: 45.5, 69.0) had the most responders at 24 months closely followed by moderate engagers (57.0%, 95% CI: 48.1, 65.6) and usual group (42.1%, 95% CI: 35.4, 49.1). It was also observed that the highest non-sustained response was in high engagers (30.3%, 95% CI: 20.2, 42.1) followed by moderate engagers (8.3%, 95% CI: 4.3, 14.2) and usual group (5.6%, 95% CI: 3.0, 9.5).

The moderate engagers (51.3%, 95% CI: 42.3, 60.1) had the highest sustained response at 24 months with respect to 0.5% reduction in HbA1c followed by high engagers (31.3%, 95% CI: 21.2, 43.1) and usual care group (27.8%, 95% CI: 21.9, 34.3).

At 36 months, sustainment of the composite outcome was the highest in the moderate engagers (27.5%, 95% CI: 19.5, 36.7) followed by the usual care (17.8%, 95% CI: 12.5, 24.2) and last by the high engagers (15.8%, 95% CI: 8.1, 26.8). There was a significant difference between the three groups at 36 months.

Depressive symptom (PHQ-9) reduction was sustained most by moderate engagers (54.0%, 95% CI: 44.2, 63.5), followed by high engagers (42.9%, 95% CI: 28.8, 57.9) and usual care group (38.0%, 95% CI: 31.0, 45.4) at 36 months. Again, the highest non-sustenance was observed in high engagers (38.1%, 95% CI: 24.6, 53.2), followed by moderate engagers (4.0%, 95% CI: 1.4, 9.2) and usual care group (1.8%, 95% CI: 0.5, 4.6).

The moderate engagers (36.2%, 95% CI: 27.0, 46.2) had the highest sustained responders at 36 months with respect to 0.5% reduction in HbA1c followed by high engagers (25.5%, 95% CI: 14.8, 39.2) and then the usual care (19.3%, 95% CI: 13.7, 25.9) group.

Table 3 shows the characteristics of participants who sustained the primary outcome after active intervention. There were no differences in the baseline characteristics of usual care and collaborative care participants who sustained the primary outcome at 24 and 36 months.

Figure 1 shows the changes in depressive symptoms (PHQ-9), FPG, HbA1c, and weight from randomisation to 36 months follow-up for the usual care group, and moderate engagers and high engagers in the intervention group. All three groups had a progressive reduction in the depressive symptoms from baseline to 36 months. However, the mean depressive symptom, which was 12.9 at baseline, decreased to 4.4 at 12 months and increased to 7.5 at 36 months in the high engagers.

Figure 1 also shows that there was reduction in the HbA1c levels in the moderate engagers and usual care from baseline to 12 months. However, by the end of the study, mean HbA1c levels at 36 months were higher than baseline (9.8% vs 8.4%, respectively) in the high engager group. There was reduction in mean FPG levels in all the three groups The high engagers had 170.9 mg/dL at baseline and had comparatively lower FPG levels during the duration of the intervention period. However, by 36 months, their FPG had increased to 167 mg/dL and was similar to that of usual care participants. The mean body weight had increased from baseline to 36 months in the moderate engager participants (68.1 kg vs 69.6 kg, respectively) and usual care (66.8 kgs vs 67.9 kg, respectively). In the high engagers, the mean body weight increased at 12 months

Table 1: Baseline Demographic Characteristics of Participants in the INDEPENDENT Trial Overall and by Intervention Exposure

Characteristic	All Participants (n=404)			Collaborative Care Group (n=196)		
	Usual Care Group n=208 (%)	Collaborative Care Group n=196 (%)	p^1	Moderate Engager (<8 visits) n=129 (%)	High Engager (≥ 8 visits) n=67 (%)	p^2
Sociodemographic characteristics						
Age						
≤49 years	33.7	37.2	0.13	34.1	43.3	0.27
50–64 years	53.8	56.1		60.5	47.8	
>64 years	12.5	6.6		5.4	9.0	
Gender (%)						
Men	36.5	45.4	0.07	39.5	56.7	0.03
Women	63.5	54.6		60.5	43.3	
Education						
Up to Secondary	76.9	78.1	0.78	79.7	74.6	0.42
More than Secondary	23.1	21.9		20.3	25.4	
Household Income						
< 10000 INR	31.7	28.1	0.68	33.3	17.9	0.06
10001–20000 INR	28.8	29.1		29.5	28.4	
> 20000 INR	39.4	42.9		37.2	53.7	
Clinical History						
History of CVD						
No	94.7	95.9	0.5	94.5	98.5	0.18
Yes	5.3	4.1		5.5	1.5	
Diabetes Duration						
< 8 years	47.1	51.0	0.42	42.5	67.2	<0.01
≥ 8 years	52.9	49.0		57.5	32.8	
Insulin use						
No	65.9	66.3	0.92	59.7	79.1	<0.01
Yes	34.1	33.7		40.3	20.9	
Micro-vascular Complications						
No	77.9	77.0	0.84	68.0	82.4	0.03
Yes	22.1	23.0		32.0	17.6	
Clinical risk factors at randomisation						
BMI (kg/m^2)						
<25 kg/m^2	35.6	36.2	0.91	36.4	35.8	0.90
25–29.9 kg/m^2	43.3	41.3		40.3	43.3	
≥30 kg/m^2	21.2	22.4		23.3	20.9	
HbA1c (%)						
<8%	30.3	27.0	0.47	17.8	44.8	<0.01
≥8%	69.7	73.0		82.2	55.2	
LDL (mg/dL)						
<130 mg/dL	73.3	79.4	0.15	82.0	74.2	0.23
≥130 mg/dL	26.7	20.6		18.0	25.8	
Triglycerides (mg/dL)						
<150 mg/dL	57.2	51.0	0.21	46.9	58.2	0.13
≥150 mg/dL	42.8	49.0		53.1	41.8	
Systolic Blood Pressure (mmHg)						
<140 mmHg	54.3	61.2	0.16	68.2	47.8	<0.01
≥140 mmHg	45.7	38.8		31.8	52.2	
Depressive Symptoms						
PHQ-9	13.4±2.5	13.0±2.5	0.36	13.1±2.6	12.9±2.3	0.53

[1]p-value from Chi-square tests comparing differences in characteristics between the collaborative care and usual care groups. [2]p-value from Chi-square tests comparing differences in characteristics between high- and low-dose intervention exposure among the collaborative care group. Moderate engagers (low-dose collaborative care) – 7 intervention visits or lesser. High engagers (high-dose collaborative care) – 8 intervention visits or more

Table 2: Participant response by intervention engagement at 12, 24, and 36 months

Time since randomisation	Response type	Usual care Group Percent (95% CI) *n*=202	Moderate engager (<8 visits) Percent (95% CI) *n*=125	High engager (≥ 8 visits) Percent (95% CI) *n*=67	*p*
12 months (after active intervention)					
Composite study outcome[#]	Responders	45.4 (38.8-52.4)	60.0 (51.3-68.3)	83.6 (73.4-91.0)	<0.001* <0.001[#] 0.011[¶] <0.001[§]
≥ 50% improvement in PHQ-9	Responders	49.0 (42.2-55.9)	66.4 (57.8-74.2)	88.1 (78.7-94.2)	<0.001* <0.001[#] 0.002[¶] <0.001[§]
≥ 0.5% reduction in HbA1c	Responders	43.6 (36.9-50.5)	66.4 (57.8-74.2)	55.2 (43.3-66.7)	<0.001* 0.127[#] <0.001[¶] 0.097[§]
≥ 5 mmHg reduction in SBP	Responders	49.5 (42.7-56.4)	50.4 (41.7-59.1)	61.2 (49.3-72.2)	0.23* 0.152[#] 0.875[¶] 0.097[§]
≥ 10 mg/dL reduction in LDL–c	Responders	40.2 (33.6-47.1)	43.2 (34.8-52.0)	43.3 (31.9-55.2)	0.83* 0.991[#] 0.594[¶] 0.657[§]
24 months (passive monitoring)					
Composite study outcome[#]	Sustained Responders	23.6 (18.0-29.9)	44.5 (35.8-53.5)	45.5 (33.9-57.4)	<0.001* <0.001[#] <0.001[¶] <0.001[§]
≥ 50% improvement in PHQ-9	Non-sustained Sustained Responders	5.6 (3.0-9.5) 42.1 (35.4-49.1)	8.3 (4.3-14.2) 57.0 (48.1-65.6)	30.3 (20.2-42.1) 57.6 (45.5-69.0)	<0.001* <0.001[#] <0.009[¶] <0.001[§]
≥ 0.5% reduction in HbA1c	Non-sustained Sustained Responders	14.6 (10.2-20.1) 27.8 (21.9-34.3)	13.4 (8.2-20.4) 51.3 (42.3-60.1)	23.9 (14.9-35.0) 31.3 (21.2-43.1)	0.014* 0.021[#] <0.001[¶] 0.124[§]
≥ 5 mmHg reduction in SBP	Non-sustained Sustained Responders	14.7 (10.3-20.2) 35.5 (27.2-40.3)	14.5 (9.2-21.5) 35.5 (27.5-44.2)	18.2 (10.3-28.7) 42.4 (31.0-54.7)	0.130* 0.375[#] 0.934[¶] 0.219[§]
≥ 10 mg/dL reduction in LDL-c	Non-sustained Sustained Responders	13.3 (9.1-18.6) 25.6 (19.9-32.1)	18.7 (12.6-26.3) 23.6 (16.7-31.6)	11.9 (5.8-21.3) 31.3 (21.2-43.1)	0.46* 0.330[#] 0.433[¶] 0.661[§]
36 months (long term monitoring)					
Composite study outcome[#]	Sustained Responders	17.8 (12.5-24.2)	27.5 (19.5-36.7)	15.8 (8.1-26.8)	<0.001* <0.001[#] <0.101[¶] <0.001[§]
≥ 50% improvement in PHQ-9	Non-sustained Sustained Responders	1.8 (0.5-4.6) 38.0 (31.0-45.4)	4.0 (1.4-9.2) 54.0 (44.2-63.5)	38.1 (24.6-53.2) 42.9 (28.8-57.9)	<0.001* <0.001[#] <0.008[¶] <0.001[§]
≥ 0.5% reduction in HbA1c	Non-sustained Sustained Responders	9.9 (6.0-15.3) 19.3 (13.7-25.9)	19.1 (12.2-28.0) 36.2 (27.0-46.2)	10.6 (4.2-21.8) 25.5 (14.8-39.2)	0.031* 0.101[#]

Contd...

Table 2: Contd...

Time since randomisation	Response type	Usual care Group Percent (95% CI) *n*=202	Moderate engager (<8 visits) Percent (95% CI) *n*=125	High engager (≥ 8 visits) Percent (95% CI) *n*=67	*P*
					<0.001¶
					0.609§
≥ 5 mmHg reduction in SBP	Non-sustained	8.0 (4.6-13.0)	8.9 (4.5-15.6)	18.0 (9.3-30.3)	0.448*
	Sustained Responders	29.0 (22.4-36.3)	29.7 (21.5-39.1)	30.0 (18.7-43.6)	0.244#
					0.954¶
					0.109§
≥ 10 mg/dL reduction in LDL-c	Non-sustained	9.8 (6.0-15.1)	6.3 (2.7-12.6)	12.3 (5.7-22.6)	0.465*
	Sustained Responders	17.2 (12.0-23.5)	18.9 (12.1-27.7)	21.1 (12.1-32.9)	0.390#
					0.609¶
					0.660§

Moderate engagers – moderate engagers of collaborative care. High engagers – high engagers of collaborative care. p-value from Pearson Chi-Square/ Fisher's Exact Test value. #Composite Study Outcome: 50% improvement in PHQ-9 plus either ≥0.5 ppt HbA1c reduction or ≥5 mmHg SBP reduction, or ≥10 mg/dL LDL-c reduction). *- Pearson Chi-Square/Fisher's Exact Test value between the three groups. #- Pearson Chi-Square/Fisher's Exact Test value for moderate engagers and high engagers. ¶- Pearson Chi-Square/Fisher's Exact Test value for control group and moderate engagers. §- Pearson Chi-Square/ Fisher's Exact Test value for control group and high engagers

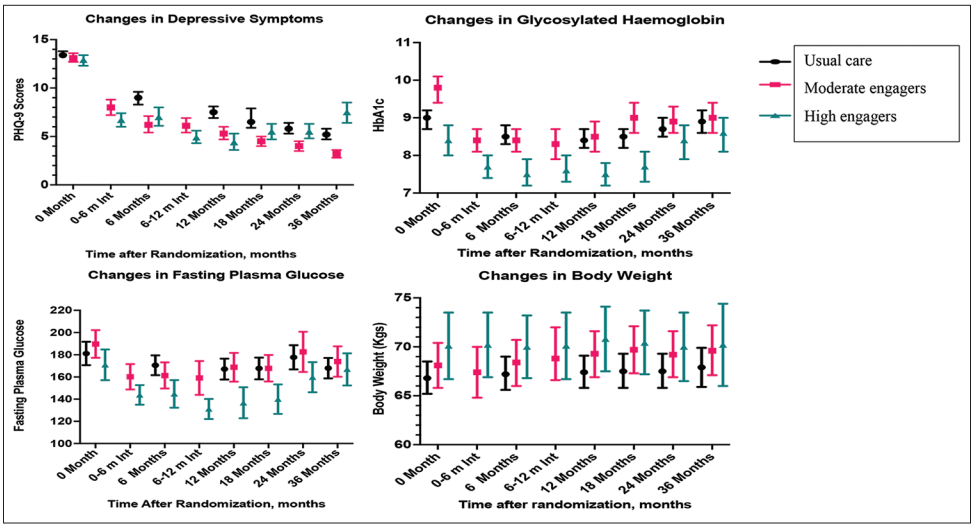

Figure 1: Changes in depressive symptoms, HbA1c, fasting blood glucose, and body weight during the study period in the INDEPENDENT study from baseline to 36 months

marginally from 70.1 kg at baseline to 70.8 kg. However, the weight stabilised to 70.2 kg and was similar to baseline at 36 months follow-up.

Discussion

We examined whether collaborative care engagement, defined as the number of study visits, had a differential impact on post-intervention outcome in patients with co-morbid depression and diabetes enrolled in the INDEPENDENT Trial. Following 12 months of active intervention, the original trial showed that the primary outcome was achieved by 71.6% and 54.7% of participants in the intervention and usual care groups, respectively, at 24 months.[23] The present study found that intervention participants who were high engagers of collaborative care had the largest proportion of responders with respect to composite outcome at 12 months (83.6%) but also the largest proportion of non-sustained response (relapse) by 24 and 36 months. Overall, intervention participants who were moderate engagers of collaborative care had more sustained response (27.5%) of composite outcome at 36 months compared with both usual care (17.8%) and high engagers (15.8%). The findings indicate that individuals who seek high engagement with collaborative care may experience more substantial waning of positive outcomes than moderate engagers and individuals receiving usual care. The results have implications for optimising care, duration, and intensity of collaborative care models for co-morbid depression and diabetes.

Longitudinal studies show that depression in diabetes is often recurrent and persistent[25–28] and depression is an ongoing disease state in patients with diabetes.[29] This study, therefore, was designed to be a comprehensive and

Table 3: Characteristics of participants who sustained composite outcome at 24 and 36 months by intervention assignment

Characteristics	24 months						36 months					
	UC *n*=45 (%±SD) Or (% and 95% CI)	CC *n*=83 (%±SD) Or (% and 95% CI)	*p*	moderate engagers *n*=53 (%±SD) Or (% and 95% CI)	high engagers *n*=30 (%±SD) Or (% and 95% CI)	*p*	UC *n*=29 (%±SD) Or (% and 95% CI)	CC *n*=37 (%±SD) Or (% and 95% CI)	*p*	moderate engagers *n*=28 (%±SD) Or (% and 95% CI)	high engagers *n*=9 (%±SD) Or (% and 95% CI)	*p*
Age	54.3±9.0	52.2±8.2	0.12	52.3±7.3	53.1±8.8	0.11	55.0±8.5	53.0±7.9	0.18	52.4±7.4	53.4±10.3	0.83
Gender (%)												
Male	28.9 (17.3–43.1)	48.2 (37.7–58.8)	0.33	39.6 (27.3–53.1)	63.3 (45.5–78.7)	0.03	20.7 (9.1–37.8)	54.1 (38.2–69.3)	0.006	57.1 (38.9–74.0)	44.4 (17.3–74.6)	0.51
Female	71.1 (56.9–82.7)	51.8 (41.2–62.3)		60.4 (46.9–72.7)	36.7 (21.3–54.5)		79.3 (62.2–90.9)	45.9 (30.7–61.8)		42.9 (26.0–61.1)	55.6 (25.4–82.7)	
Education (%)												
Secondary or Less	73.3 (59.3–84.5)	75.9 (65.9–84.1)	0.75	79.2 (67.0–88.4)	70.0 (52.3–84.0)	0.49	79.3 (62.2–90.9)	70.3 (54.4–83.1)	0.41	67.9 (49.5–82.8)	77.8 (45.6–95.1)	0.57
More than Secondary	26.7 (15.5–40.7)	24.1 (15.9–34.1)		20.8 (11.6–33.0)	30.0 (16.0–47.7)		20.7 (9.1–37.8)	29.7 (16.9–45.6)		32.1 (17.2–50.5)	22.2 (4.9–54.4)	
Household Income (%)												
<10000 INR	22.2 (12.0–35.8)	28.9 (20.0–39.3)	0.71	35.8 (24.0–49.2)	16.7 (6.7–32.7)	0.11	24.1 (11.5–41.6)	27.0 (14.8–42.7)	0.87	28.6 (14.5–46.8)	22.2 (4.9–54.4)	0.79
10001–20000 INR	31.1 (19.1–45.5)	27.7 (19.0–38.0)		28.3 (17.6–41.3)	26.7 (13.5–44.1)		34.5 (19.3–52.6)	37.8 (23.6–53.9)		39.3 (23.0–57.7)	33.3 (10.4–65.2)	
>20000 INR	46.7 (32.7–61.1)	43.3 (33.1–54.1)		35.8 (24.0–49.2)	56.7 (39.0–73.1)		41.4 (25.0–59.4)	35.1 (21.3–51.2)		32.1 (17.2–50.0)	44.4 (17.3–74.6)	
Diabetes Duration (%)												
<8 years	60.0 (45.4–73.3)	59.8 (49.0–69.9)	0.97	53.8 (40.4–66.9)	70.0 (52.3–84.0)	0.15	58.6 (40.6–75.0)	55.6 (39.4–70.8)	0.80	55.6 (37.1–72.9)	55.6 (25.4–82.7)	1.0
≥8 years	40.0 (26.7–54.6)	40.2 (30.1–51.0)		46.2 (33.1–59.6)	30.0 (16.0–47.7)		41.4 (25.0–59.4)	44.4 (29.2–60.6)		44.0 (27.1–62.9)	44.0 (17.3–74.6)	

CC – Collaborative Care. UC – Usual Care. moderate engagers - moderate engagers of collaborative care. high engagers - high engagers of collaborative care. *p* - Pearson Chi-Square/Fisher's Exact Test value

holistic longitudinal assessment of outcomes following collaborative care for co-morbid depression and diabetes. While collaborative care is recommended for persons with co-morbid depression and diabetes[30] and has been evaluated in many settings, most collaborative studies have followed up for up to 24 months. Very few studies have followed up participants for 36 months or longer. The strength of this study was the tracking of cardio-metabolic parameters and depressive symptoms at various time points over the study duration of 3 years, making it one of the longest follow-up studies in India.

Although the high engager group ostensibly received more attention, they did not sustain the improvement at the end of 36 months. The most likely explanation is that these patients had the most intensive treatment and were more likely to have severe symptoms or complex depression or chronic/severe psychosocial stressors, and they sought out or were advised to make more visits. During active collaborative care, this group in fact showed the strongest benefit of intervention. However, high engagers showed the strongest decline after the withdrawal of the intervention at 12 months, suggesting that collaborative care was not able to permanently resolve their needs. A stepped collaborative care approach[31] or an approach that tailors the intensity and duration of the intervention based on depressive symptom scores at randomisation could provide greater benefits to those in most need.[32]

Several past studies on collaborative care for depression show beneficial outcomes for up to 12 months after intervention, with lesser benefits after the end of active intervention. The CADET study, which studied the clinical effectiveness of collaborative care for depression in UK among 581 adults, found that collaborative care improved depression immediately after treatment compared with usual care and the effects of collaborative care persist up to 12 months follow-up.[33] In the IMPACT study, Hunkeler *et al*.[34] found that collaborative care delivered long-term improvements for up to 24 months, but with reduced benefits at 18 and 24 months. We add to these findings by examining engagement in care as a modifier of treatment response immediately after and months following the end of active intervention. Specifically, high engagers in INDEPENDENT study were the most responsive to treatment and collaborative care at the end of 12 months of intervention, yet this same group had greater relapse (non-subsentence) at 24 months and 36 months. In fact, in a collaborative care intervention that ran for 24 months, Rost *et al*.[35] reported that the intervention significantly improved both symptoms and functioning at 24 months, increasing remission by 33%. This is one of the highest improvements reported so far and strengthens the case for longer running intervention for sustained effect.

Relapse in depressive symptoms has been reported for many treatments. Jarrett *et al*.[36] studied high risk participants for relapse of depression. They found that although relapse risk was reduced by cognitive therapy or anti-depressants, the effect was not sustained, suggesting that some higher-risk patients may require alternate longer-term interventions. Lustman[26] observed that even for those who improved during the clinical trial, relapse to symptomatic major depression occurred rapidly as nearly 60% of patients were depressed within the first year in a 5-year follow-up study. Given that roughly one-third of patients in our study exhibited relapse (non sustainence) in depressive symptoms by 24 months irrespective of study group and the worst relapse was observed in the high engagers, it may be safe to say that some individuals may do better with low doses of collaborative care for longer duration. For patients who have had two or more episodes of depression, in fact, the current relapse prevention interventions recommended by NICE are a minimum of 2 years treatment with anti-depressant medication. However, patients with three episodes or more of depression may need higher *intensity* interventions, such as high-intensity mindfulness-based cognitive therapy (MBCT) or high-intensity individual cognitive behavioural therapy (CBT) for patients who have relapsed despite anti-depressant medication.[37]

At the end of 36 months, the body weight has increased, compared to the baseline in moderate engagers group and the usual care groups. The reason could be an improved glycaemic status (HbA1c) in both arms at the end of 3 years in comparison to the high engagers group. The participants in the high engagers group had higher values of the depressive scores and cardio-metabolic parameters compared to the moderate engagers group and the usual care group at the end of 36 months. As mentioned earlier, this could be due to that more attention was given to participants who had higher depressive symptom scores and/or higher metabolic parameters. Other reasons could be lack of motivation[38] or lack of self-care, adherence to diet, and exercise.[39]

Moriarty *et al*.[40] suggested that patients and health care professionals would benefit greatly from a robust clinical tool that could risk-stratify patients and then target relapse prevention measures to those at higher risk. Prior episodes of depressive symptoms should be examined for relapse prevention, according to the opinion of previous researchers.[40,41] The INTERPRET–DD study, which studied depression and diabetes in 14 countries, found that amongst the participants, 4.6% had recurrent depression and 16.6% had persistent depression. The majority of those with major depressive disorder (MDD), also known as clinical depression (72.5%), had moderate to severe depressive symptoms. The INTERPRET-DD study used various tools to assess the mental health status of participants.[42] This may be an indicator that the use of a single tool may be inadequate and more tools may be required to assess depressive symptoms and ensure adequate engagement of participants for collaborative care and prevent relapse.

The strengths of this study include long follow-up in a developing country, a fairly large sample size, very low attrition, and a diverse population. Additionally, this study

used non-mental health professional to make a positive impact and address gaps in mental health delivery. Finally, the targets set for the study were clinically significant (such as 0.5% reduction in A1c levels) and could be accomplished compared to tight control (such as A1c <7.0%). Despite the strengths of the longitudinal design and carefully measured outcomes, the study had some limitations. Firstly, it was done in urban clinics with specialists available at each centre. Whether this will work in rural settings is not clear. Secondly, collaborative care models are complex interventions which consist of a number of separate elements, where the particular elements that function as the 'active ingredient' can be difficult to identify.[43] In this study also, we could not identify the active ingredient in collaborative care, which is another limitation, although the outcomes showed that collaborative care is superior to usual care. Finally, we were also able to explain the differences noted between the moderate and high engagers.

The US *Institute of Medicine's* "Crossing the Quality Chasm" report emphasised that to improve quality of care for chronic illnesses, "trying harder will not work, changing systems of care will".[44] This holds good across health care delivery systems and also in the Indian context. More research is needed to evaluate treatment of different depression subtypes in people with diabetes; the cost-effectiveness of therapies, the utilisation of health-care resources, the need to account for cultural differences and diverse health-care systems, and novel treatment and prevention approaches are all factors to be considered.[45] INDEPENDENT study and its findings may be the step in the right direction to fulfil the above in India and developing countries.

Conclusion

This is the first collaborative care study of this sort in India. In the INDEPENDENT study, collaborative care, when compared to usual care, had a strongly positive effect on improving depression and cardio-metabolic indicators at the end of the 12-month intervention. Benefits of collaborative care were the largest in participants with moderate engagement compared with high engagement, although a majority of participants relapsed on one or more outcome measures by 36 months. Since it was not identified which individual intervention component was effective, more research is needed to understand or predict which patients will do well with a brief course of collaborative care and who will need intervention for longer periods. Although the study was effective in urban diabetes clinics, more studies are needed in rural areas, which often lack the support of specialist doctors and infrastructure. Finally, if the beneficial effects are to be sustained, persons with co-morbid depression and diabetes may need light touch interventions for longer periods and longer-term assistance to maintain health and reduce depressive symptoms. Future research should aim at minimal cost-effective intervention for co-morbid depression and diabetes that sustains over longer periods of time.

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Conflicts of interest

There are no conflicts of interest.

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