Cost-Effectiveness of a Collaborative Care Model Among Patients With Type 2 Diabetes and Depression in India

https://doi.org/10.2337/dc21-2533

Karl M.F. Emmert-Fees,[1,2,3,4,5] Michael Laxy,[1,2,3,5] Shivani A. Patel,[3] Kavita Singh,[6] Subramani Poongothai,[7] Viswanathan Mohan,[7] Lydia Chwastiak,[8] K.M. Venkat Narayan,[3] Rajesh Sagar,[9] Aravind R. Sosale,[10] Ranjit Mohan Anjana,[7] Gumpeny R. Sridhar,[11] Nikhil Tandon,[12] and Mohammed K. Ali[3,13]

OBJECTIVE

To assess the cost-effectiveness of collaborative versus usual care in adults with poorly controlled type 2 diabetes and depression in India.

RESEARCH DESIGN AND METHODS

We performed a within-trial cost-effectiveness analysis of a 24-month parallel, open-label, pragmatic randomized clinical trial at four urban clinics in India from multipayer and societal perspectives. The trial randomly assigned 404 patients with poorly controlled type 2 diabetes (HbA_{1c} ≥8.0%, systolic blood pressure ≥140 mmHg, or LDL cholesterol ≥130 mg/dL) and depressive symptoms (9-item Patient Health Questionnaire score ≥10) to collaborative care (support from nonphysician care coordinators, electronic registers, and specialist-supported case review) for 12 months, followed by 12 months of usual care or 24 months of usual care. We calculated incremental cost-effectiveness ratios (ICERs) in Indian rupees (INR) and international dollars (Int'l-$) and the probability of cost-effectiveness using quality-adjusted life-years (QALYs) and depression-free days (DFDs).

RESULTS

From a multipayer perspective, collaborative care costed an additional INR309,558 (Int'l-$15,344) per QALY and an additional INR290.2 (Int'l-$14.4) per DFD gained compared with usual care. The probability of cost-effectiveness was 56.4% using a willingness to pay of INR336,000 (Int'l-$16,654) per QALY (approximately three times per-capita gross domestic product). The willingness to pay per DFD to achieve a probability of cost-effectiveness >95% was INR401.6 (Int'l-$19.9). From a societal perspective, cost-effectiveness was marginally lower. In sensitivity analyses, integrating collaborative care in clinical workflows reduced incremental costs by ∼47% (ICER 162,689 per QALY, cost-effectiveness probability 89.4%), but cost-effectiveness decreased when adjusting for baseline values.

CONCLUSIONS

Collaborative care for patients with type 2 diabetes and depression in urban India can be cost-effective, especially when integrated in clinical workflows. Long-term cost-effectiveness might be more favorable. Scalability across lower- and middle-income country settings depends on heterogeneous contextual factors.

Physical and mental conditions share multiple physiological and behavioral pathways (1,2), leading to an increased risk for mental health comorbidities, such as

[1]Institute of Epidemiology, Helmholtz Zentrum München, Neuherberg, Germany
[2]German Center for Diabetes Research (DZD), Neuherberg, Germany
[3]Hubert Department of Global Health, Emory University, Atlanta, GA
[4]Institute for Medical Information Processing, Biometry and Epidemiology, Ludwig-Maximilians-Universität München, Munich, Germany
[5]Department of Sports and Health Sciences, Technical University of Munich, Munich, Germany
[6]Centre for Chronic Conditions and Injuries, Public Health Foundation of India and Centre for Chronic Disease Control, New Delhi, India
[7]Madras Diabetes Research Foundation and Dr. Mohan's Diabetes Specialities Centre, Chennai, Tamil Nadu, India
[8]Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA
[9]Department of Psychiatry, All India Institute of Medical Sciences, New Delhi, India
[10]Diabetes Care and Research Center, DIACON Hospital, Bangalore, Karnataka, India
[11]Endocrine and Diabetes Centre, Visakhapatnam, India
[12]Department of Endocrinology and Metabolism, All India Institute of Medical Sciences, New Delhi, India
[13]Department of Family and Preventive Medicine, Emory University, Atlanta, GA, United States

Corresponding author: Karl M.F. Emmert-Fees, karl.emmert-fees@helmholtz-muenchen.de

Received 8 December 2021 and accepted 10 October 2022

This article contains supplementary material online at https://doi.org/10.2337/figshare.21308028.

depression and anxiety, among patients with chronic conditions (3,4). Among people with type 2 diabetes, depression is twice more common than among people without type 2 diabetes. Furthermore, comorbid depression is associated with an elevated risk for micro- and macrovascular complications (5,6), higher mortality (7), worse self-management (8), and higher costs (9).

The syndemic of type 2 diabetes and depression is particularly pervasive in lower- and middle-income countries (LMICs), where in India, for example, the prevalence is estimated to be >30% (10). In LMICs, a large proportion of mental health disorders remain undiagnosed and untreated, producing a large economic burden for individuals, families, and health systems (11–14). Integrated, collaborative care can address these challenges in caring for people with comorbid mental and physical chronic conditions (15–17).

Especially in resource-limited settings, disease management needs are often unmet because of lack of universal health care coverage and barriers to care through large physical distances, fragmented services by specialists, and an overall shortage of health care professionals. Hence, there is a need for accessible, cost-effective, integrated chronic disease care (18–21). For LMICs, some evidence on the cost-effectiveness of integrated mental health care exists (22), yet economic evaluations of interventions for patients with physical chronic and concurrent mental conditions are lacking to guide health policy and clinical practice in these countries (23).

Previously, we showed that compared with usual care, a 12-month culturally adapted collaborative care intervention, which integrated care for patients with type 2 diabetes and depression in four diverse urban diabetes clinics in India, was associated with a 30% higher likelihood of achieving sustained, clinically significant improvements in composite depressive symptoms and cardiometabolic indices at 24 months (15,24). Here, we evaluated the within-trial cost-effectiveness of this culturally adapted collaborative care intervention.

RESEARCH DESIGN AND METHODS

The Integrating Depression and Diabetes Treatment (INDEPENDENT) study was a multicenter, open-label, pragmatic, patient-randomized controlled trial conducted at four socioeconomically diverse urban diabetes clinics in India. The ethics committees of all involved institutions approved the study, and eligible patients gave written informed consent before they were enrolled. Detailed methods have been published elsewhere (15).

Trial Design and Intervention Description

To be eligible for inclusion, patients had to be at least 35 years of age and have a confirmed diagnosis of type 2 diabetes, moderate to severe depressive symptoms (9-item Patient Health Questionnaire [PHQ-9] score ≥10 [range 0–27] where higher scores indicate more severe depressive symptoms), and at least one poorly controlled cardiometabolic marker (hemoglobin A_{1c} [HbA_{1c}] ≥8%, systolic blood pressure ≥140 mmHg, or LDL cholesterol ≥130 mg/dL).

Clinic staff reviewed medical records at the four clinics (private clinics in Chennai, Bangalore, and Visakhapatnam and a large public hospital in Delhi) from 9 March 2015 to 31 May 2016 to identify eligible patients on the basis of cardiometabolic parameters and screened them using the PHQ-9. Blinded study staff randomized eligible, consenting patients in blocks of 4, 6, 8, or 10, stratified by site, using an electronic data management system. Patients in the intervention group received collaborative care for 12 months and were followed for 12 additional months without intervention. The collaborative care intervention consisted of three evidence-based components at the patient (e.g., self-management support), clinician (e.g., electronic decision support), and system (e.g., patient case reviews) level. A care team at each clinic implemented these components to supplement usual care by diabetes physicians. Each team consisted of a full-time nonphysician care coordinator who had no previous training in mental health management and specialists (psychiatrist and diabetologist) who served as consultants and provided advice during case review meetings. All teams received a 3-day in-person training on the intervention, and care coordinators received additional training on management of patients with depression, including reinforcement through monthly coaching calls with the study team. Extensive information on the intervention is available elsewhere (15,25).

The control group received usual care over 24 months. Treating physicians were notified of their patients' depressive symptoms and received basic training in suicide risk assessment and management.

Data Collection and Follow-up

All patients were followed for 24 months. Patients in both groups attended baseline and 6 monthly assessments, which were paid for by the study. All costs of clinical care between study assessments were borne by the respective payers (patient out of pocket, health insurance, or government-funded clinics).

Information on depressive symptoms was collected during all study visits using the PHQ-9 and the 20-item Symptoms Checklist Depression Scale (SCL-20) (range 0–4, with higher scores indicating worse symptoms). To measure health status from a patient perspective (i.e., health utility), data on health-related quality of life was collected at the baseline and 24-month study visit using the Health Utilities Index Mark 3 (HUI-3) (range −0.36 to 1.00, with higher values indicating higher utility) with its standard Canadian value set. The HUI-3 measures eight different attributes of health-related quality of life (e.g., vision, ambulation, cognition), is robust across populations, and has been validated in East Asian populations (26,27). Information on the various cost components was collected at baseline, 12 months, and 24 months using pilot-tested questionnaires (28).

Design of Economic Evaluation

We performed within-trial cost-effectiveness analyses comparing collaborative care with usual care over 24 months from multipayer and societal perspectives. The multipayer perspective included costs occurring directly in the formal health sector (e.g., clinic visits), independent of the actual payer, and out-of-pocket expenses in the informal health sector (e.g., food during inpatient visits). It comprised costs borne by health care providers (i.e., public hospitals) and private health insurance (i.e., reimbursement of patient-reported expenses) as well as out-of-pocket expenditures by patients. The multipayer approach is especially useful in LMIC settings with a high heterogeneity of payers (29). The societal perspective further

included all other costs in the informal health sector, such as patient time costs for care and lost productivity due to outpatient care (Supplementary Material 1).

All costs were measured in Indian rupees (INR), with 2015 as the base year, and converted to purchasing power parity adjusted for international dollars (Int'l-$) with an exchange rate of INR20.18 per Int'l-$ based on the average exchange rates over 2015–2018 (30). Costs and health effects were discounted at 5% per year, which is recommended for LMICs because of higher rates of economic growth (31).

We followed a hybrid costing approach to calculate cumulative costs over the 24-month study period. Data sources included *1*) self-report on health care utilization and expenditure for both groups; *2*) health care utilization, care coordinator interactions, and case review meetings recorded in the decision-support electronic health record system during the active intervention period for the intervention group only; and *3*) costs, resource use, and time spent on intervention-related activities from a survey among clinic staff (Supplementary Material 2). Self-reported costs over the previous 6 months were doubled to reflect annual costs. We added 10% overhead and fringe benefit costs to intervention setup and delivery costs, except commodities (e.g., laptops). An extensive description is available in Supplementary Material 3. This study was conducted and reported according to current guidelines for cost-effectiveness research in health and medicine (32,33) (Supplementary Material 4–5).

Cost Components

Formal Health Sector: Screening

Total costs related to screening were calculated by multiplying the number of potentially eligible individuals (n = 1,905) identified through clinical records by the time and associated labor costs (10 min × wage) a care coordinator needs per individual to screen for depressive symptoms using the PHQ-9. Per-patient screening costs were calculated by dividing total costs related to screening by the number of randomly assigned patients. To reflect that screening would be required to identify eligible patients in a real-world setting (i.e., screen and treat), screening costs were only applied to intervention group participants.

Formal Health Sector: Intervention Setup and Delivery

Costs related to intervention setup and delivery consisted of two components: *1*) fixed costs for care coordinator training (onsite and online), one laptop per site, educational materials, and care coordinator salaries for 12 months and *2*) care team labor costs for case review meetings, including time spent by psychiatrists and diabetologists. Corresponding time use and unit costs were based on the clinic staff survey (Supplementary Table 1*A* and *B*).

We also, separately, investigated the cost containment potential of integrating the intervention into existing clinical workflows by costing care coordinator labor on the basis of actual time spent delivering the intervention (including time for administrative tasks and coordination with specialists) and the inclusion of the cost for development and implementation of the decision-support electronic health record system (Supplementary Material 6).

Formal Health Sector: Health Care Utilization

Costs related to health care utilization comprised those for outpatient care, inpatient care, and medications. Outpatient care was defined as the number of clinic visits, tests, and examinations. We calculated unit costs for all sites as the median value of self-reported cost per item (e.g., consultation fee, HbA_{1c} test) across the three private sites and cross checked these estimates with the clinic staff survey to ensure the reliability of our approach. To capture outpatient resource use in the intervention group during the active intervention period, we leveraged data on received care recorded in the decision-support electronic health record system. For all other periods and the control group, we had to rely on self-reported data. We analyzed the influence of this differential costing approach on the results in a sensitivity analysis (Supplementary Material 5). For inpatient costs only, self-reported costs for hospital stays due to type 2 diabetes–related complications could be calculated, as no other information on inpatient health care utilization was available. Medication costs were calculated using self-reported expenses.

Informal Health Sector: Time, Lost Productivity, Food, and Transportation Costs

Patient and escort expenses for food and transportation during hospital stays (food is usually not provided during hospital stays in India) were based on self-report. We estimated patient time cost with questions capturing time spent for diabetes care and patient wages. For both outpatient and inpatient care, time costs of escorts were estimated based on the self-reported number of visits the patient was accompanied and the respective escorts' wages. We assumed a full workday of escort commitment for each escort visit as a conservative estimate to account for round-trip travel time to the clinic and waiting times. Following a human capital approach, patient lost productivity was estimated on the basis of self-reported workdays missed because of outpatient care, assuming an 8-h workday (Supplementary Material 3).

Health Effects

We used quality-adjusted life years (QALYs) and depression-free days (DFDs) to measure health utility and effects. Health status as measured by the HUI-3 was transformed to health utilities and used to estimate QALYs, a measure that incorporates quality and length of life in a single metric. Since 1 QALY indicates 1 year in perfect health (health utility = 1), we calculated accumulated QALYs per patient as the area under the health utility curve over the 24-month study period. Because the HUI-3 was only administered at baseline and 24 months, we linearly interpolated health utilities between these two time points (Supplementary Material 7).

We calculated DFDs on the basis of PHQ-9 score and, alternatively, the SCL-20 depression symptoms score as suggested by Vannoy et al. (34). To calculate DFDs, depression severity at baseline and all 6 monthly study visits was defined using two instrument-specific threshold scores. Patients were assumed to be free of depression (DFD = 1) if below these thresholds (PHQ-9 score <5, SCL-20 score <0.5) and fully depressed (DFD = 0) if above (PHQ-9 score >14, SCL-20 score >1.34). Thresholds are defined according to the literature except for the upper limit of the SCL-20 score, which was defined using the mean SCL-20 score for patients at baseline (34). If the respective score was between thresholds, linear interpolation was used to convert scores into proportionate DFDs between 0 and 1. The final estimate of DFDs accumulated by patients is the number of days between

assessment time points multiplied by the respective level of depression (between 0 and 1), which is equivalent to the area under the depression severity curve over time. To achieve this, we linearly interpolated depression severity between study visits (Supplementary Material 7).

Statistical Analysis

We conducted the primary analysis from a multipayer perspective. Secondary analyses were conducted separately from a societal perspective and stratified by clinic. We estimated between-group differences in cumulative costs over 24 months based on average marginal effects using generalized linear models with a γ-distribution and a logarithmic link function (35). Because the logarithm of 0 is undefined, arbitrary costs of INR10.0 were added to all participants with zero costs. Between-group differences in QALYs and DFDs after 24 months were estimated using linear regression models. For all outcomes, we estimated unadjusted differences in costs between the intervention and usual care groups. In the adjusted sensitivity analysis, we controlled for baseline values of outcomes. We calculated incremental cost-effectiveness ratios (ICERs) and constructed cost-effectiveness acceptability curves (CEACs) for each health outcome and costing perspective. Uncertainty in ICERs was computed using a bootstrap procedure with 1,000 replications.

Self-reported data on outpatient health care utilization was missing for up to 20.30% of observations at baseline, 22.52% at 12 months, and 25.74% at 24 months. To account for these missing data and facilitate intention-to-treat analyses, we merged available self-reported economic data with 10 imputation data sets that were previously constructed for the primary effectiveness analysis (15). We next imputed each merged data set fivefold, for a total of 50 imputation data sets (Supplementary Material 8). All statistical procedures were based on these 50 imputation data sets, and results were combined following convention (i.e., Rubin's rules) (36).

As no official willingness-to-pay threshold for QALYs exists in India, we used guidance from the World Health Organization Choosing Interventions That Are Cost-Effective initiative, which recommends a threshold of one to three times the country-specific gross domestic product (GDP) per capita (37). This resulted in thresholds between INR112,000 (Int'l-$5,552) and INR336,000 (Int'l-$16,654) per QALY based on India's average per-capita GDP of Int'l-$6,041 from 2015 to 2018 (30,38) (Supplementary Material 9). Similarly, no established willingness-to-pay threshold exists for DFDs. To enable interpretation of the related CEACs, we calculated the theoretical willingness to pay per DFD that would be needed to achieve a prespecified probability of cost-effectiveness that was ≥95%.

All analyses were conducted in R version 4.0.3 (39). Statistical tests were two-sided and used a significance threshold of 5%. Where appropriate, 95% CIs are reported.

Sensitivity Analyses

We performed sensitivity analyses to explore the influences of our costing decisions and to check the robustness of our results. These included a cost containment analysis in which the intervention is assumed to be integrated in clinical workflows, adjustment for baseline values of outcomes, adoption of a health system perspective, use of self-reported data on health care utilization for both groups, inclusion of costs for development and implementation of the decision-support electronic health record system, and a two-way missing-not-at-random analysis in which costs are varied by ±15% and QALYs by 15% to account for potential over- or underestimation. Each analysis is described in detail in Supplementary Material 6.

RESULTS

Patient Characteristics

In total, 1,905 patients were screened for eligibility. Of 404 randomly assigned patients, 196 were allocated to receive the collaborative care intervention and 208 to receive usual care (Supplementary Fig. 1). Patient characteristics in both groups were similar at baseline. Mean (SD) health utility was 0.66 (0.26) in the intervention group and 0.62 (0.25) in the control group. Baseline costs across categories were also similar between groups (Supplementary Table 2).

Cost Components

Considering all cost components, patients in the intervention group accumulated mean (SD) total costs of INR48,287 (15,799) (Int'l-$2,393 [783.1]) compared with INR20,920 (12,933) (Int'l-$1,037 [641.1]) in the control group over the 24-month study period. A descriptive overview of cost components by group is presented in Table 1. Unadjusted between-group differences in costs are presented in Table 2.

Formal Health Sector: Intervention and Screening

Screening administered by care coordinators to identify eligible patients costed INR181 (Int'l-$8.97) per patient. On average, the intervention costed INR21,836 (Int'l-$1,082) per patient in the intervention group (Table 1). Of these, INR3,850 (Int'l-$190.8) were upfront costs associated with intervention setup (e.g., training workshops, laptops). The largest share of intervention costs accrued during intervention delivery, of which salaries for care coordinators constituted the most expensive component (INR14,661 [Int'l-$726.7]) (Table 1).

Formal Health Sector: Health Care Utilization

Health care utilization was the most expensive nonintervention cost component (Table 1). Patients in the intervention group had INR3,926 (95% CI 1,881–5,971) (Int'l-$194.6 [93.3–296.0]) higher health care utilization costs compared with the control group, particularly because of outpatient care. Medication costs and costs due to inpatient care were similar between groups (Tables 1 and 2).

Informal Health Sector

Costs related to food, transportation, time, and lost productivity were largely similar between groups (Table 1). Although we observed slightly higher time costs (INR808.6 [95% CI −367.5 to 1,985]) (Int'l-$40.1 [−18.2 to 98.4]) and lost productivity (INR468.1 [−537.4 to 1,474]) (Int'l-$23.2 [−26.7 to 73.0]) in the intervention group, which were both driven by outpatient care, the respective estimates were subject to considerable uncertainty (Table 2).

Health Effects

Over 24 months, patients in the intervention group gained more QALYs and DFDs compared with the control group (Table 1). The unadjusted between-group difference in QALYs was 0.084 (95% CI 0.015–0.152). The between-group difference in DFDs was 89.5 (62.8–116.2) using PHQ-9

Table 1—Descriptive mean costs, utility, and effectiveness outcomes in the collaborative care (intervention) and usual care (control) groups after 24 months

	Collaborative care				Usual care			
	INR		Int'l-$		INR		Int'l-$	
	Mean	SD†	Mean	SD†	Mean	SD†	Mean	SD†
Costs types and components								
Formal health sector costs related to the intervention*								
Intervention setup								
Central training workshop for CCs	1,903	0.00	94.4	0.00	0.00	0.00	0.00	0.00
Onsite training and quality assurance	1,315	0.00	65.2	0.00	0.00	0.00	0.00	0.00
Webinar service for CCs over 24 months	260.6	0.00	12.9	0.00	0.00	0.00	0.00	0.00
One laptop per site	370.2	0.00	18.4	0.00	0.00	0.00	0.00	0.00
Intervention delivery								
Educational materials	272.1	0.00	13.5	0.00	0.00	0.00	0.00	0.00
CC salaries	14,661	0.00	726.7	0.00	0.00	0.00	0.00	0.00
Case review meetings	3,054	0.00	151.4	0.00	0.00	0.00	0.00	0.00
Subtotal	21,836	0.00	1,082	0.00	0.00	0.00	0.00	0.00
Formal health sector costs related to health care utilization								
Outpatient visits and care	10,946	6,532	542.6	323.8	6,865	6,024	340.3	298.6
Inpatient visits and care	978.8	6,242	48.5	309.4	567.6	5,920	28.13	293.5
Medication	8,268	7,481	409.8	370.8	8,834	7,462	437.9	369.9
Subtotal	20,193	10,285	1,001	509.8	16,267	9,839	806.3	487.7
Formal health sector costs related to screening‡								
Depression screening by clinical staff	181.0	0.00	8.97	0.00	0.00	0.00	0.00	0.00
Subtotal	181.0	0.00	8.97	0.00	0.00	0.00	0.00	0.00
Informal health sector costs								
Food and transportation§								
Food costs for inpatient visits	41.7	353.3	2.06	17.5	24.9	201.5	1.23	9.99
Transportation costs for inpatient visits	54.1	266.0	2.68	13.2	38.6	278.0	1.91	13.8
Food and transportation cost of escorts for inpatient visits	181.2	1,022	8.98	50.7	66.5	518.4	3.30	25.7
Time costs and lost productivity								
Escort time costs for inpatient visits	529.0	5,935	26.2	294.2	317.9	3,180	15.8	157.6
Escort time costs for outpatient visits	905.7	3,067	44.9	152.0	359.9	1,462	17.8	72.5
Patient time costs for diabetes care	2,478	2,023	122.8	100.3	2,426	2,264	120.3	112.2
Lost productivity due to outpatient care	1,888	6,448	93.6	319.6	1,420	3,484	70.4	172.7
Subtotal	6,077	10,099	301.2	500.6	4,654	6,414	230.7	317.9
Total	48,287	15,799	2,393	783.1	20,920	12,933	1,037	641.1
Health effects								
QALYs	1.31	0.34			1.23	0.35		
DFDs (PHQ-9)	487.3	111.7			397.8	155.5		
DFDs (SCL-20)	477.0	146.3			363.4	182.2		

Costs and health effects discounted at 5% per year. CC, care coordinator. *Accumulated throughout the 0–12-month intervention period. †An SD of 0 indicates that the respective cost component was the same for all individuals. ‡One-time cost for intervention group patients at baseline. §The items food costs for inpatient visits and transportation costs for inpatient visits were included in the analysis from the multipayer perspective to reflect that these were directly paid by patients. The item food and transportation cost of escorts for inpatient visits was only included in the analysis from the societal perspective. See Supplementary Material 1 and 4 for further definition of costing perspectives.

and 113.6 (81.2–146.0) using SCL-20 (Table 2, Fig. 1, Supplementary Table 3, and Supplementary Fig. 2).

Cost-Effectiveness

From a multipayer perspective, mean costs in the intervention group were INR25,975 (95% CI 23,916–28,035) (Int'l-$1,288 [1,549–1,753]) higher than in the control group. The intervention costed INR309,558 (Int'l-$15,344) per QALY and between INR290.2 (Int'l-$14.4) and INR228.7 (Int'l-$11.3) per DFD gained based on the PHQ-9 and SCL-20, respectively (Table 3 and Supplementary Table 3).

For QALYs, the probability that the intervention is cost-effective was 0.80–56.4% using willingness-to-pay thresholds from INR112,000 (Int'l-$5,552) to INR336,000 (Int'l-$16,654). The required willingness-to-pay per DFD to achieve a probability of cost-effectiveness >95% was INR401.6 (Int'l-$19.9) (Table 3 and Fig. 1). From a societal perspective, cost-effectiveness was only marginally lower for all outcomes (Table 3 and Fig. 1).

Sensitivity Analyses

Cost-effectiveness decreased when adjusting for baseline values, particularly because of a reduction in the estimated between-group difference in QALYs (Table 3, Supplementary Tables 3–5, and Supplementary Figs. 2 and 3). Stratified analyses showed moderate differences among clinics, albeit patients at one clinic gained no QALYs in the adjusted sensitivity analysis (statistically nonsignificant) (Supplementary Table 6*A*).

Our findings were sensitive to some costing decisions. Particularly in the cost containment analysis, which assumed that care coordinators were integrated into clinical workflows so that their labor costs were based on actual time spent

Table 2—Unadjusted incremental costs, utility, and effectiveness outcomes of collaborative vs. usual care after 24 months

	Incremental difference between intervention and control			
	INR, mean	95% CI	Int'l-$, mean	95% CI
Cost estimates: formal health sector				
Costs related to screening	181	—	8.97	—
Costs related to intervention setup and delivery	21,836	—	1,082	—
Costs related to health care utilization	3,926	1,881 to 5,971	194.6	93.3 to 296.0
Cost estimates: informal health sector				
Food and transportation costs*	147.0	−77.6 to 371.6	7.29	−3.85 to 18.4
Time costs	808.6	−367.6 to 1,985	40.1	−18.2 to 98.4
Lost productivity due to outpatient care	468.0	−537.4 to 1,474	23.2	−26.6 to 73.0
Utility and effectiveness estimates				
QALYs, mean (95% CI)	0.084	0.015 to 0.152		
DFDs (PHQ-9), mean (95% CI)	89.5	62.8 to 116.2		
DFDs (SCL-20), mean (95% CI)	113.6	81.2 to 145.9		

Costs and health effects discounted at 5% per year. *Includes both patient's and escort's food and transportation costs for inpatient visits (see Table 1). In the analysis from the multipayer perspective, only the patient's food and transportation costs for inpatient visits were included (incremental mean difference between intervention and control: INR32.3 [Int'l-$1.60]). For further explanation, see Supplementary Material 1 and 4.

delivering the intervention instead of annual dedicated full-time salaries, the per-patient intervention costs reduced to INR9,510 (Int'l-$471.4) (Supplementary Table 7). In this scenario, incremental costs were reduced by ∼47% (Supplementary Table 8), and the probability of cost-effectiveness increased to 15.1–89.4% depending on the respective willingness-to-pay threshold (results not shown). However, including costs for the development of the decision-support electronic health record system led to a decrease in cost-effectiveness. When relying solely on self-reported cost data for both groups, cost-effectiveness of the intervention increased, rendering our costing decision in the main analysis to the more conservative approach (Supplementary Table 5*A* and *B*). The two-way missing-not-at-random analysis indicated a large cost-effectiveness potential of the intervention if QALYs are truly underestimated and costs overestimated but further highlights that cost-effectiveness might be substantially lower when baseline health utility is adjusted for (Fig. 1 and Supplementary Fig. 2).

CONCLUSIONS

In this within-trial economic evaluation of a culturally adapted 12-month collaborative care intervention targeting patients with type 2 diabetes and depression at four diverse urban diabetes clinics in India, we found that collaborative care can be cost-effective over 24 months, especially when integrated into existing clinical workflows. Integrating mental health services in primary care in LMICs is effective, yet there is a paucity of economic evaluations of integrated care models for patients with chronic conditions and mental comorbidities (22). The original effectiveness analysis of the INDEPENDENT trial demonstrated improvements in depressive symptoms and cardiometabolic indices in patients seeking care in diabetes clinics (15). In contrast, the Integrated mHealth System for the Prevention and Care of Chronic Disease (mWELLCARE) trial aimed to assess the effectiveness of an integrated care model for the management of hypertension, type 2 diabetes, and depression in government primary clinics in India but found no benefit (40).

Studies from the U.S. and U.K. that investigated collaborative care in comparable patient populations reported similar, albeit larger, improvements in health-related quality of life and smaller incremental costs. The Team Approach to Improve the Quality of Diabetes Care for Patients With Schizophrenia (TEAMcare) study in Washington State investigated the effectiveness of a patient-centered, team-based collaborative care management intervention in patients with depressive disorder and poorly controlled type 2 diabetes or coronary heart disease over 24 months (41). Patients in the intervention group achieved substantial gains in (regression-based) QALYs (0.335 [95% CI −0.18 to 0.85]) and DFDs (114 [79–149]). The intervention in TEAMcare was cost-saving over 24 months (16). A comparable intervention and evaluation was applied in the 24-month cost-effectiveness analysis of the U.K. Collaborative Interventions for Circulation and Depression (COINCIDE) trial, including patients with depression and type 2 diabetes or coronary heart disease (42). Here, collaborative care resulted in 0.136 (0.061–0.212) additional QALYs and incremental costs of £1,777 (95% CI −320 to 3,875) (ICER £13,069 per QALY) (42). The reduction of the incremental intervention cost by ∼50% in our cost containment analysis, which, similar to TEAMcare, replicates a costing approach based on actual care coordinator-patient interactions, supports that collaborative care is very likely to be cost-effective if integrated in existing clinical workflows.

Setting up patient-centered collaborative care is resource intensive and presupposes an essential infrastructure, such as patient registries and electronic records (43). It is therefore crucial to distinguish between upfront implementation and long-run operating costs. Keeping this in mind, we explored the impact of our costing and analysis decisions to provide an overall picture of the cost-effectiveness of collaborative care for patients with type 2 diabetes and depression in India, which may be informative for future extensions in LMICs. On a sidenote, our findings and implications did not change when applying alternative discount rates (results not shown).

We show that a 12-month collaborative care intervention can have sustained effects and is cost-effective at 24 months, yet the current follow-up prohibits an

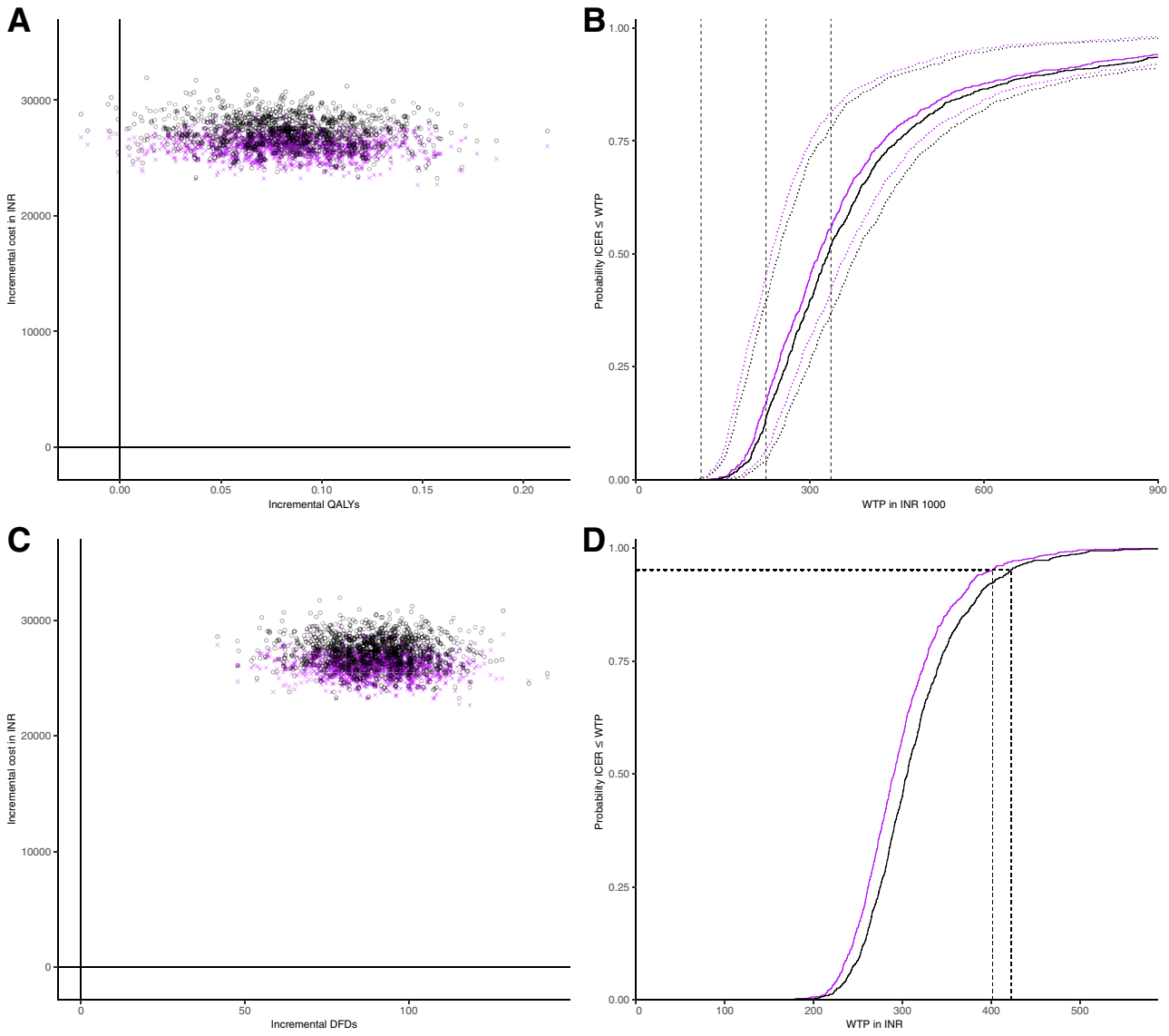

Figure 1—Incremental cost-effectiveness planes and acceptability curves of collaborative care vs. usual care after 24 months from the multipayer perspective (purple) and societal perspective (black). *A*: Cost-effectiveness plane for QALYs from unadjusted analysis. Large plus sign indicates the mean ICER estimates. *B*: CEACs for QALYs from unadjusted analysis. Three vertical dashed lines represent willingness-to-pay (WTP) thresholds based on one to three times the GDP of India (INR112,000–336,000). Dotted lines represent lower and upper boundaries of the CEACs based on the missing-not-at-random sensitivity analysis for both multipayer and societal perspectives. *C*: Cost-effectiveness plane for DFDs from unadjusted analysis. Large plus sign indicates the mean ICER estimates. *D*: CEACs for DFDs from unadjusted analysis. Dashed vertical lines represent WTP thresholds that would result in at least 95% probability of cost-effectiveness for both multipayer and societal perspectives. Costs and health effects discounted at 5% per year.

extrapolation of the long-term health effects, costs, and thus, cost-effectiveness because of the uncertainty in the clinical trajectory of both groups. Short-term (re)intervention after deterioration of symptoms and corresponding longer depression-free states and improved health-related quality of life may lead to substantial gains in QALYs. Additionally, reductions in the long-term per-patient costs of the intervention are likely due to the amortization of fixed costs, such as training, increased efficiency in clinical workflows, and declining technology costs.

Because of high integration and resource requirements, the scalability and adaptability of collaborative care across diverse local settings remain important challenges. Implementation in clinics of different types, sizes, and locations, with heterogeneous patient populations exhibiting specific patterns of multimorbidity (including infectious diseases), may presume the modification of specific (expensive) intervention components, such as in-person case review meetings. This is aggravated by a severe global shortage of mental health care professionals, especially in LMICs and even more so in rural areas (44).

Our study has several strengths. It is the first to provide evidence of which circumstances collaborative care for patients with chronic physical conditions and mental comorbidities could be cost-effective in an LMIC setting. We captured context-specific economic impacts of the intervention, such as escort costs, and used Int'l-$ to make our estimates comparable across countries. To measure patient benefits of the intervention, we used QALYs and two DFD measures

Table 3—Unadjusted and adjusted cost-effectiveness results of collaborative care vs. usual care after 24 months

	Δ-costs			ICER		Probability of		ICER		WTP per DFD to achieve probability of cost-effectiveness >95%	
Cost perspective	INR (95% CI)	Int'l-$ (95% CI)	Δ-QALYs (95% CI)	INR	Int'l-$	cost-effectiveness, %*	Δ-DFDs† (95% CI)	INR	Int'l-$	INR	Int'l-$
Unadjusted analysis											
Multipayer	25,975 (23,916 to 28,035)	1,288 (1,549 to 1,753)	0.084 (0.015 to 0.152)	309,558	15,344	0.80–56.4	89.5 (62.8 to 116.2)	290.2	14.4	401.6	19.9
Societal	27,367 (24,476 to 30,257)	1,357 (1,577 to 1,863)		326,140	16,166	0.80–52.6		305.8	15.2	422.1	20.9
Adjusted analysis											
Multipayer	26,156 (24,112 to 28,200)	1,297 (1,559 to 1,763)	0.032 (−0.003 to 0.068)	813,658	40,331	0.00–2.21	79.5 (55.2 to 103.8)	329.1	16.3	449.7	22.3
Societal	27,616 (24,759 to 30,474)	1,369 (1,592 to 1,876)		859,073	42,582	0.00–2.20		347.5	17.2	481.3	23.9

Costs and health effects discounted at 5% per year. Δ, incremental difference between intervention and control group; WTP, willingness to pay. *WTP ranged from INR112,000 to −336,000. †Based on PHQ-9.

as clinically relevant outcomes. Finally, we explored the sensitivity of our results to a variety of costing approaches, analysis decisions, and implementation scenarios, exploring their influence on cost-effectiveness.

Our study also has several limitations. First, because of the pragmatic nature of the trial and the heterogeneity in the Indian health system, detailed assessments of health care utilization or validation of self-reported information using patient or insurance records was infeasible. We therefore relied on consistently collected self-reported data for many cost components, including medications; notably, these were no different between groups at baseline. Second, we did not account for costs of restructuring diabetes care to integrate collaborative care in existing clinical workflows in the cost containment analysis. These results, therefore, constitute a lower cost-effectiveness bound. Third, albeit an HUI-3 value set to calculate health utilities among high-income Asian populations exists, no corresponding value set for LMIC settings is available. Fourth, health utility was not collected at the 12-month visit, where the largest between-group difference was expected according to the clinical effectiveness analysis and the association between depressive symptoms and health-related quality of life (15,45). Therefore, underestimation of the incremental QALYs is likely. As a potential consequence of this, the intervention was unlikely to be cost-effective in the adjusted sensitivity analysis because of a smaller incremental difference in QALYs. However, considering the potential underestimation of QALYs and the results from the cost containment analysis, this does not affect the main conclusion of our study. Fifth, a substantial amount of economic data was missing. We conducted missing-not-at-random analyses to account for this further uncertainty in costs in conjunction with the missing health utility measurement at 12 months. Sixth, data on depression-related inpatient costs were not available. However, this is unlikely to affect our results in a meaningful way because patients with already prevalent severe depression and other psychiatric disorders were not eligible for the trial, and depression-related serious adverse events were very rare (15). Finally, we were only able to include lost productivity due to outpatient care but not to illness.

Collaborative care, as applied in the INDEPENDENT trial, could be cost-effective to treat patients with type 2 diabetes and depression in urban India, particularly if integrated into routine clinical workflows. This analysis can serve as guidance for the integration of mental health and chronic disease care in other LMIC settings. From a long-term perspective, cost-effectiveness of the intervention is likely to be more favorable but might be affected by heterogeneity in implementation feasibility because of contextual factors across diverse local settings.

Funding. This study was funded by the National Institute of Mental Health (grant R01MH100390).

The National Institute of Mental Health had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and the decision to submit the manuscript for publication.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. K.M.F.E.-F., M.L., S.A.P., K.S., S.P., V.M., L.C., and M.K.A. conceptualized and revised the design of the study. K.M.F.E.-F., M.L., K.S., L.C., and M.K.A. were responsible for the analysis and interpretation of the data. S.A.P., K.S., V.M., R.S., A.R.S., R.M.A., G.R.S., and N.T. critically revised and provided feedback on the interpretation of the data. K.M.F.E.-F., M.L., and M.K.A. prepared the initial manuscript draft. All authors reviewed, edited, and approved the final manuscript. V.M., L.C., K.M.V.N., and M.K.A. obtained funding for this work. K.M.F.E.-F. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented in abstract form at the 16th Symposium of the International Diabetes Epidemiology Group, 29 November–1 December 2019, Seoul, South Korea.

References

1. Golden SH, Lazo M, Carnethon M, et al. Examining a bidirectional association between depressive symptoms and diabetes. JAMA 2008; 299:2751–2759

2. Tabák AG, Akbaraly TN, Batty GD, Kivimäki M. Depression and type 2 diabetes: a causal association? Lancet Diabetes Endocrinol 2014;2: 236–245

3. Mezuk B, Eaton WW, Albrecht S, Golden SH. Depression and type 2 diabetes over the lifespan: a meta-analysis. Diabetes Care 2008;31:2383–2390

4. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. Diabetes Care 2001;24:1069–1078

5. Poongothai S, Anjana RM, Pradeepa R, et al. Association of depression with complications of type 2 diabetes–the Chennai Urban Rural

Epidemiology Study (CURES-102). J Assoc Physicians India 2011;59:644–648
6. de Groot M, Anderson R, Freedland KE, Clouse RE, Lustman PJ. Association of depression and diabetes complications: a meta-analysis. Psychosom Med 2001;63:619–630
7. Hofmann M, Köhler B, Leichsenring F, Kruse J. Depression as a risk factor for mortality in individuals with diabetes: a meta-analysis of prospective studies. PLoS One 2013;8:e79809
8. Gopichandran V, Lyndon S, Angel MK, et al. Diabetes self-care activities: a community-based survey in urban southern India. Natl Med J India 2012;25:14–17
9. Egede LE, Bishu KG, Walker RJ, Dismuke CE. Impact of diagnosed depression on healthcare costs in adults with and without diabetes: United States, 2004-2011. J Affect Disord 2016;195:119–126
10. Poongothai S, Anjana RM, Radha S, Sundari BB, Shanthi Rani CS, Mohan V. Epidemiology of depression and its relationship to diabetes in India. J Assoc Physicians India 2017;65:60–66
11. Mendenhall E, Kohrt BA, Norris SA, Ndetei D, Prabhakaran D. Non-communicable disease syndemics: poverty, depression, and diabetes among low-income populations. Lancet 2017;389:951–963
12. Garin N, Koyanagi A, Chatterji S, et al. Global multimorbidity patterns: a cross-sectional, population-based, multi-country study. J Gerontol A Biol Sci Med Sci 2016;71:205–214
13. Arokiasamy P, Uttamacharya U, Jain K, et al. The impact of multimorbidity on adult physical and mental health in low- and middle-income countries: what does the study on global ageing and adult health (SAGE) reveal? BMC Med 2015;13:178
14. World Health Organization. *mhGAP: Mental Health Gap Action Programme: Scaling Up Care for Mental, Neurological and Substance Use Disorders*. Geneva, World Health Organization, 2008
15. Ali MK, Chwastiak L, Poongothai S, et al.; INDEPENDENT Study Group. Effect of a collaborative care model on depressive symptoms and glycated hemoglobin, blood pressure, and serum cholesterol among patients with depression and diabetes in India: the INDEPENDENT randomized clinical trial. JAMA 2020;324:651–662
16. Katon W, Russo J, Lin EHB, et al. Cost-effectiveness of a multicondition collaborative care intervention: a randomized controlled trial. Arch Gen Psychiatry 2012;69:506–514
17. Coventry P, Lovell K, Dickens C, et al. Integrated primary care for patients with mental and physical multimorbidity: cluster randomised controlled trial of collaborative care for patients with depression comorbid with diabetes or cardiovascular disease. BMJ 2015;350:h638
18. Thornicroft G, Ahuja S, Barber S, et al. Integrated care for people with long-term mental and physical health conditions in low-income and middle-income countries. Lancet Psychiatry 2019;6:174–186
19. World Health Organization. *Mental Health Action Plan 2013–2020*. Geneva, World Health Organization, 2013
20. Yesudian CAK, Grepstad M, Visintin E, Ferrario A. The economic burden of diabetes in India: a review of the literature. Global Health 2014;10:80
21. Mills A. Health care systems in low- and middle-income countries. N Engl J Med 2014;370:552–557
22. Cubillos L, Bartels SM, Torrey WC, et al. The effectiveness and cost-effectiveness of integrating mental health services in primary care in low- and middle-income countries: systematic review. BJPsych Bull 2021;45:40–52
23. Dang A, Likhar N, Alok U. Importance of economic evaluation in health care: an Indian perspective. Value Health Reg Issues 2016;9:78–83
24. Rao D, Lipira L, Kumar S, et al. Input of stakeholders on reducing depressive symptoms and improving diabetes outcomes in India: formative work for the INDEPENDENT study. Int J Noncommun Dis 2016;1:65–75
25. Kowalski AJ, Poongothai S, Chwastiak L, et al. The Integrating Depression and Diabetes Treatment (INDEPENDENT) study: design and methods to address mental healthcare gaps in India. Contemp Clin Trials 2017;60:113–124
26. Furlong WJ, Feeny DH, Torrance GW, Barr RD. The Health Utilities Index (HUI) system for assessing health-related quality of life in clinical studies. Ann Med 2001;33:375–384
27. Qian X, Tan RL, Chuang LH, Luo N. Measurement properties of commonly used generic preference-based measures in East and South-East Asia: a systematic review. Pharmaco-Economics 2020;38:159–170
28. Shah S, Singh K, Ali MK, et al.; CARRS Trial Writing Group. Improving diabetes care: multi-component cardiovascular disease risk reduction strategies for people with diabetes in South Asia–the CARRS multi-center translation trial. Diabetes Res Clin Pract 2012;98:285–294
29. Islek D, Weber MB, Ranjit Mohan A, et al. Cost-effectiveness of a stepwise approach vs standard care for diabetes prevention in India. JAMA Netw Open 2020;3:e207539
30. Organisation for Economic Co-operation and Development. Purchasing power parities (PPP) (indicator). Accessed 15 November 2021. Available from https://data.oecd.org/conversion/purchasing-power-parities-ppp.htm
31. Haacker M, Hallett TB, Atun R. On discount rates for economic evaluations in global health. Health Policy Plan 2020;35:107–114
32. Neumann PJ, Ganiats TG, Russell LB, Sanders GD, Siegel JE. *Cost-Effectiveness in Health and Medicine*. New York, Oxford University Press, 2016
33. Husereau D, Drummond M, Petrou S, et al.; CHEERS Task Force. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. BMJ 2013;346:f1049
34. Vannoy SD, Arean P, Unützer J. Advantages of using estimated depression-free days for evaluating treatment efficacy. Psychiatr Serv 2010;61:160–163
35. Glick HA, Doshi JA, Sonnad SS, Polsky D. *Economic Evaluation in Clinical Trials*. New York, Oxford University Press, 2014
36. Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. New York, John Wiley & Sons, 2004
37. Tan-Torres Edejer T, Baltussen R, Adam T, et al. *Making Choices in Health: WHO Guide to Cost-effectiveness Analysis*. Geneva, World Health Organization, 2003
38. World Bank. GDP per capita, PPP (current international $) - India. Accessed 15 November 2021. Available from https://data.worldbank.org/indicator/NY.GDP.PCAP.PP.CD?end=2021&name_desc=true&start=2021&view=map
39. R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria, R Foundation for Statistical Computing, 2021
40. Prabhakaran D, Jha D, Prieto-Merino D, et al.; Members of the Research Steering Committee, Investigators, Members of the Data Safety and Monitoring Board. Effectiveness of an mHealth-Based electronic decision support system for integrated management of chronic conditions in primary care: the mWellcare cluster-randomized controlled trial. Circulation 2019;139:380–391
41. Katon WJ, Lin EH, Von Korff M, et al. Collaborative care for patients with depression and chronic illnesses. N Engl J Med 2010;363:2611–2620
42. Camacho EM, Davies LM, Hann M, et al. Long-term clinical and cost-effectiveness of collaborative care (versus usual care) for people with mental-physical multimorbidity: cluster-randomised trial. Br J Psychiatry 2018;213:456–463
43. McGinty EE, Daumit GL. Integrating mental health and addiction treatment into general medical care: the role of policy. Psychiatr Serv 2020;71:1163–1169
44. Pattanayak RD, Sagar R. Depressive disorders in Indian context: a review and clinical update for physicians. J Assoc Physicians India 2014;62:827–832
45. Katon WJ. Epidemiology and treatment of depression in patients with chronic medical illness. Dialogues Clin Neurosci 2011;13:7–23