Circulation

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Effectiveness of an mHealth-Based Electronic Decision Support System for Integrated Management of Chronic Conditions in Primary Care

The mWellcare Cluster-Randomized Controlled Trial

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Dorairaj Prabhakaran, MD, DM, MSc
Dilip Jha, MSc
David Prieto-Merino, PhD
Ambuj Roy, MD, DM
Kavita Singh, MSc, PhD
Vamadevan S. Ajay, MPH, PhD
Devraj Jindal, MPH
Priti Gupta, MBBS, MD
Dimple Kondal, MSc, PhD
Shifalika Goenka, MBBS, PhD
Pramod Jacob, MBBS, MSc
Rekha Singh, MBBS
B. G. Prakash Kumar, MBBS
Pablo Perel, MD, MSc, PhD
Nikhil Tandon, MD, PhD
Vikram Patel, MBBS, MSc, PhD

BACKGROUND: The burden of noncommunicable diseases and their risk factors has rapidly increased worldwide, including in India. Innovative management strategies with electronic decision support and task sharing have been assessed for hypertension, diabetes mellitus, and depression individually, but an integrated package for multiple chronic condition management in primary care has not been evaluated.

METHODS: In a prospective, multicenter, open-label, cluster-randomized controlled trial involving 40 community health centers, using hypertension and diabetes mellitus as entry points, we evaluated the effectiveness of mWellcare, an mHealth system consisting of electronic health record storage and an electronic decision support for the integrated management of 5 chronic conditions (hypertension, diabetes mellitus, current tobacco and alcohol use, and depression) versus enhanced usual care among patients with hypertension and diabetes mellitus in India. At trial end (12-month follow-up), using intention-to-treat analysis, we examined the mean difference between arms in change in systolic blood pressure and glycated hemoglobin as primary outcomes and fasting blood glucose, total cholesterol, predicted 10-year risk of cardiovascular disease, depression score, and proportions reporting tobacco and alcohol use as secondary outcomes. Mixed-effects regression models were used to account for clustering and other confounding variables.

RESULTS: Among 3698 enrolled participants across 40 clusters (mean age, 55.1 years; SD, 11 years; 55.2% men), 3324 completed the trial. There was no evidence of difference between the 2 arms for systolic blood pressure (Δ=–0.98; 95% CI, –4.64 to 2.67) and glycated hemoglobin (Δ=0.11; 95% CI, –0.24 to 0.45) even after adjustment of several key variables (adjusted differences for systolic blood pressure: – 0.31 [95% CI, –3.91 to 3.29]; for glycated hemoglobin: 0.08 [95% CI, –0.27 to 0.44]). The mean within-group changes in systolic blood pressure in mWellcare and enhanced usual care were –13.65 mm Hg versus –12.66 mm Hg, respectively, and for glycated hemoglobin were –0.48% and –0.58%, respectively. Similarly, there were no differences in the changes between the 2 groups for tobacco and alcohol use or other secondary outcomes.

CONCLUSIONS: We did not find an incremental benefit of mWellcare over enhanced usual care in the management of the chronic conditions studied.

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Key Words: decision support techniques ■ diabetes mellitus ■ hypertension ■ primary health care ■ telemedicine

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Clinical Perspective

What Is New?

- This trial demonstrated that mWellcare, an mHealth system consisting of a clinical decision support system and storage of electronic health records, combined with enhanced usual care led to a reduction in systolic blood pressure and glycohemoglobin that was not significantly different from enhanced usual care alone in patients with hypertension and diabetes mellitus in primary care settings.
- The participants in the mWellcare arm also did not differ significantly on the secondary outcomes of fasting blood glucose, total cholesterol, predicted 10-year risk of cardiovascular diseases, depression score, or proportions reporting tobacco and alcohol use; however, the mWellcare arm had higher self-reported adherence to medications.

What Are the Clinical Implications?

- This trial demonstrates the feasibility of an ambitious multifactorial electronic health record– and electronic decision support–based mHealth intervention across multiple sites at the primary care level using available trained staff.
- The overall null result, likely resulting from benefits achieved in the enhanced usual care arm, emphasizes the potential value of leveraging nonphysician providers and improving access to needed medications.
- National health policymakers in low- and middle-income countries, including India, can use this information to inform decisions surrounding the rollout of widespread public health interventions.

The burden of noncommunicable diseases (NCDs), including mental health conditions, and their associated risk factors has rapidly increased worldwide, including in India.[1,2] A recent estimate suggests a US $2.32 trillion loss in national income in India between 2012 and 2030 resulting from cardiovascular disease (CVD) and diabetes mellitus.[3] The rapid rise in chronic disease burden, population aging, severe shortage of skilled healthcare providers, and inadequately developed health systems together impose huge constraints on healthcare services in India.[4]

To better tackle the growing burden of chronic conditions and their risk factors, the 1978 Alma Ata declaration endorsed strengthening primary care to improve health outcomes and the equitable distribution of healthcare services at low cost in the population.[5] Barriers that accentuate evidence to practice gaps include patient-level factors (low levels of awareness, low adherence to medications and healthy lifestyle), physician-level factors (limited time, clinical inertia), and system-level factors (inadequately trained workforce, lack of health record keeping, lack of access to affordable generic medicines).[6–9] Innovations at the primary care level with the use of mobile phone technologies and task sharing by trained nurses can empower, encourage, and facilitate care processes as well as strengthen healthcare delivery systems by overcoming these barriers.[10,11]

Systematic reviews and meta-analyses of studies evaluating the role of an electronic decision support (EDS) system for the management of chronic conditions show a paucity of well-designed studies on patient outcomes.[12,13] Furthermore, previous studies were either pilot studies or studies that evaluated the effectiveness of EDS and nonphysician healthcare providers in managing single disease conditions (hypertension or diabetes mellitus).[14–16] To the best of our knowledge, an integrated mHealth-based EDS system addressing multiple chronic conditions (hypertension, diabetes mellitus, depression, tobacco and alcohol use) collectively remains untested in India. Therefore, using hypertension and diabetes mellitus as entry points, we evaluated the effectiveness of a nurse-facilitated, mHealth-based EDS for the integrated management of 5 chronic conditions in primary care settings of India through the mWellcare trial.

METHODS

The data, analytical methods, and study materials will be made available on request to other researchers for purposes of reproducing the results or replicating the procedure. Data will be available at Public Health Foundation of India's Central Research Data Repository 6 months after completion of the study (July 2019).[17]

Study Design

The mWellcare trial was a pragmatic, open-label, cluster-randomized controlled clinical trial in which community health centers (CHCs) were randomized to receive the mHealth-based EDS or enhanced usual care (EUC). We recruited eligible consenting participants with a confirmed diagnosis of hypertension or diabetes mellitus from 40 CHCs between April 5 and August 21, 2016. The last date of follow-up was September 30, 2017. The trial methods have been previously published.[18] This study received ethics committee approval from the Public Health Foundation of India and London School of Hygiene and Tropical Medicine. The study was also cleared by the Indian Health Ministry Screening Committee. All participants provided written informed consent to participate. The study was conducted according to the study protocol (Method 1 in the online-only Data Supplement) and analyzed according to the statistical analysis plan (Method 2 in the online-only).

Study Setting and Participants

We recruited 20 CHCs each in Haryana (North India) and Karnataka (South India) for the trial. A CHC caters to a rural population of ≈80 000 to 120 000 and serves as a referral center for 4 primary health centers in the public healthcare delivery system.[19] We selected the CHCs from 4 districts in Haryana and 2 districts in Karnataka that were covered under the National

Program for the Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases, and Stroke (NPCDCS). The NPCDCS, launched in 2008 in select districts, is a governmental program that focuses on the prevention and control of major NCDs through health promotion, early diagnosis, management, and referral of cases, strengthening infrastructure and capacity building.[20] Under the NPCDCS, an NCD nurse was recommended to be used for the management of patients at the outpatient NCD clinic in each CHC. Of 40 selected CHCs, NCD nurses appointed under NPCDCS were available in only 10 CHCs in Karnataka before this study. Therefore, NCD nurses supported from trial funds were appointed at the remaining 30 selected CHCs.

Participants were eligible if they were ≥30 years of age, intended to reside in the catchment area of CHCs for ≥1 year, and had been diagnosed with hypertension with systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or type 2 diabetes mellitus with fasting blood glucose ≥140 mg/dL or postprandial blood glucose ≥200 mg/dL. Pregnant women, patients with type 1 diabetes mellitus, patients requiring immediate referral to tertiary care because of accelerated hypertension or diabetic complications, patients with learning difficulties or vision or hearing impairments, and patients with malignancy or other life-threatening conditions were excluded from the study.

Randomization, Treatment Assignments, and Blinding

The CHC served as the unit of randomization. An independent biostatistician performed central computer-based randomization of CHCs stratified by states (Haryana and Karnataka) and within each state by the availability of NCD nurses recruited under NPCDCS. Given the nature of the cluster-randomized trial design, neither personnel nor participants were blinded to the intervention. Assessments at study end were carried out by independent outcome assessors. The study biostatistician remained blinded throughout the study until the database was locked, at which point the study was fully unblinded.

Intervention

The intervention was developed by adapting existing clinical management guidelines to the local context, development, and validation of clinical algorithms and pilot testing of the mWellcare system.[21–26] The mWellcare system was an Android application built on the CommCare platform. Details of the mWellcare system, platform, and its development and testing are published elsewhere.[27] Briefly, the mWellcare system was designed to generate EDS recommendations for the management of hypertension and diabetes mellitus, comorbid depression, and alcohol and tobacco use, tailored to the participant's profile and risk level. It stored the health records electronically, enabling long-term monitoring and follow-up. It was also equipped to send short message service reminders (to take medication and attend follow-up visits) to patients.

In the intervention group (mWellcare arm), we provided centralized training on the current clinical management guidelines to all physicians. In addition, onsite training for orientation to the mWellcare system was conducted at each site. For NCD nurses, we provided training in the management of hypertension, diabetes mellitus, depression, and tobacco and alcohol use. In addition, 3 days of training were provided to nurses on using the mWellcare system. This training was supplemented by another 2 days of onsite supervision and support. In all mWellcare arm sites, simplified charts on the management of these conditions were displayed prominently.

In the mWellcare arm, the NCD nurse used a tablet computer installed with the mWellcare system to collect data on patient history, blood pressure, blood glucose, depression, tobacco and alcohol use, and current medications. From this patient-specific clinical information, the mWellcare system generated a decision support recommendation (DSR) for the physician. The DSR printout summarized information on patient profile, diagnosed condition, comorbid conditions, and previous and current medications and recommended a treatment plan for the 5 chronic conditions based on standard guidelines (Figures I and II in the online-only Data Supplement). The DSR also provided a lifestyle modification advisory and date for the next follow-up visit. After reviewing the DSR, the physician either agreed with the recommendations or suggested changes in the treatment plan that were recorded in the mWellcare system by the NCD nurse. Next, the physician referred the patient to the NCD nurse, who provided lifestyle advice using the prompts of the DSR. In addition, the nurse provided pamphlets (in the local language) to each participant. Participants were followed up for 12 months. At every scheduled follow-up visit, the patients' clinical parameters were recorded to generate a longitudinal trend/summary by the mWellcare system. In addition, participants received short message service reminders for scheduled follow-up visits and medication adherence. Each mWellcare site received a monthly report on the number of participants reporting for the scheduled follow-up and the average change in clinical parameters at the CHC level.

Enhanced Usual Care

In the EUC alone arm, we provided training to physicians on the clinical management guidelines for hypertension and diabetes mellitus. In addition, as with the mWellcare arm, charts on the management of these conditions were displayed prominently at the outpatient clinics. We also conducted the NCD nurses' training in the management of hypertension and diabetes mellitus. To balance both study arms, we provided the EUC NCD nurses with a tablet computer (without the mWellcare system) for collecting data at the baseline visit. Physicians in the EUC arm managed their patients with the assistance of NCD nurses, according to their clinical judgment. In addition, the EUC arm NCD nurses provided and explained the lifestyle advice pamphlet (in local languages, Hindi and Kannada) to each participant. Follow-up in the EUC arm was at the discretion of the treating physicians.

Outcomes

The primary study outcomes were the between-group differences in mean change (from baseline to 1 year) in SBP and glycated hemoglobin (HbA_{1c}) among participants with hypertension and diabetes mellitus, respectively. The secondary outcomes included the between-group difference in mean change (from baseline to 1 year) in fasting plasma glucose, total cholesterol, predicted 10-year risk of CVD with the recalibrated Framingham risk score, tobacco use, body mass

index, and alcohol use. Depression score was measured only at the end-of-study evaluation. The Framingham Risk Score was recalibrated to the Indian population with the methodology suggested by Chow et al.[28] To generate the values for recalibration, we used World Health Organization data on yearly estimates of CVD mortality in India (2012) and the average values of risk factors in the CARRS study (Centre for Cardiometabolic Risk Reduction in South Asia).[29]

Data Collection

Blood pressure was measured with automated blood pressure monitors (Omron HEM 907), height was measured with a stadiometer (Seca 213), and weight was measured with a digital weighing machine (Seca 813). Blood samples for HbA_{1c} and total cholesterol were analyzed at laboratories that had accreditation from the National Accreditation Board for Testing and Calibration Laboratories. Capillary blood was used to measure fasting blood glucose with a glucometer. Information about tobacco use and physical activity (with the modified CARRS questionnaire) was obtained in both arms.[29] Depression was diagnosed with the Patient Health Questionnaire-9, and alcohol consumption (with the Alcohol Use Disorder Identification Test) was assessed only in the mWellcare arm.[30,31] At the end-of-study assessment, the Alcohol Use Disorder Identification Test questionnaire and Patient Health Questionnaire-9 were used to measure alcohol use and depression, respectively, in both arms.

We conducted a rigorous process evaluation in the trial. Trained research staff using a structured observation checklist conducted periodic monitoring visits of trial sites to assess the fidelity of the intervention. Information on contextual factors such as the availability of common antihypertensive drugs, antihyperglycemic drugs, statin, and aspirin was collected from each CHC every fortnight by the research staff. Data on follow-up visits and agreement of physicians with the DSR were obtained from the mWellcare system server database. At study end, participants reported adherence to medications in the week before the clinic visit (values ranging from 0–7 days) and perceived quality of care (medicine availability, guidance from the physician, quality of care, frequency of blood pressure measurement, and care provided by the NCD nurse). We also conducted in-depth interviews with patients, NCD nurses, and physicians at the end of the trial to obtain information on perceived barriers and facilitators that influenced the uptake of the intervention.

Sample Size

This study was powered for the primary outcomes of between-group difference in mean change in SBP and HbA_{1c} from baseline to 1 year. Sample size calculation was based on the assumption that recruitment of 40 participants with hypertension per cluster in 40 clusters would yield >98% power to detect a true mean difference of 4 mm Hg in the Δ change in SBP between the mWellcare and EUC arms, assuming a 15 mm Hg SD of the change in both arms with a type I error of 5% and an intraclass correlation of 0.05.[15] Similarly, 40 participants with diabetes mellitus per cluster would yield a power >99% for detecting a true difference in the average change of HbA_{1c} between the 2 arms of 0.37%, assuming a 1.1% SD of the changes in both arms and an intraclass correlation of 0.04.[29,32] To adhere to the previous statistical power and assuming a 20% loss to follow-up, we proposed enrolling 3600 participants, that is, 90 participants at each of the 40 CHCs selected in the trial. All calculations were based on the formula for the comparison of 2 means in cluster-randomized trials proposed by Hayes and Bennett.[33]

Statistical Analysis

The primary analyses followed the intention-to-treat principle. We analyzed each continuous outcome separately with

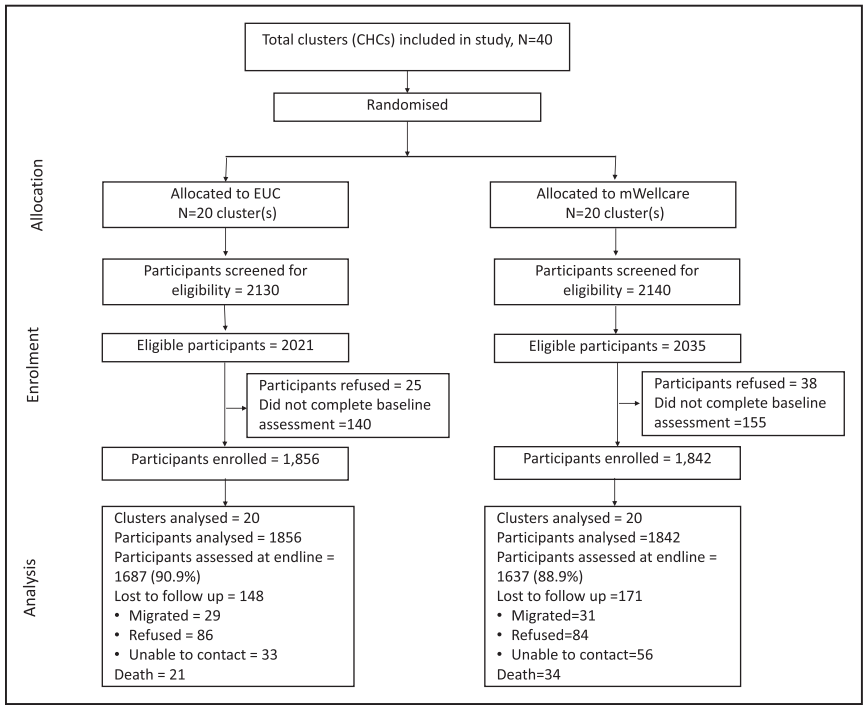

Figure 1. CONSORT (Consolidated Standards for Reporting Trials) flow diagram.
CHC indicates community health center; and EUC, enhanced usual care.

a linear mixed model in which the dependent variable was the difference in the outcome (after minus before), and the main explanatory variable was the trial arm. We included a random effect of the CHC to account for the clustered design. Each model was adjusted by baseline outcome values in 2 ways: the patient's regression to the mean effect was controlled by including the distance to the CHC mean of the patient's baseline outcome value, and the baseline outcome means of the CHC was included to control for baseline differences between CHCs.

The secondary outcomes that were dichotomous (tobacco and alcohol use) were analyzed at the CHC level as a change in the proportion of positive responses adjusted by baseline proportions. We estimated adjusted and unadjusted models on the basis of logistic regressions weighted by CHC sample size.

In the adjusted models for each outcome (primary or secondary), we first examined the effect of each potential confounder by controlling for it separately, and only those that had a value of $P>0.1$ and caused a change in the trial effect by >10% were included in a multivariable-adjusted model. Each outcome variable was adjusted by a different set of potential confounders.

For the 2 main outcomes (SBP and HbA_{1c}), we performed a sensitivity analysis of the adjusted models with multiple imputations of missing data (Table I in the online-only Data Supplement). We imputed 5 data sets and calculated the mean effect using the Rubin rules. In the imputation equations, we included all baseline variables that had an association with the probability of missing in the outcome with a value of $P<0.1$ and did not have >40% missing data to improve outcome imputation. The substantive model, however, included only the same variables as the adjusted model without multiple imputations.

Subgroup analysis of the 2 main outcomes in each of the candidate variables (z) was done as a 2-step process. We first reestimated the unadjusted trial effect in the outcome (as in the main trial analysis) stratified by z, obtaining a separate effect (and standard error) in each stratum of z. We then did a meta-analysis of these effects across strata and computed the Q statistic for heterogeneity and its *P* value. This way of

Table 1. Baseline Characteristics of Study Participants by Treatment Arm

Baseline Characteristics	EUC Arm (n=1856)	mWellcare Arm (n=1842)	SMD
Participants with hypertension, n (%)	932 (50.2)	906 (49.2)	–0.021
Participants with diabetes mellitus, n (%)	625 (33.7)	683 (37.1)	0.071
Participants with both conditions, n (%)	299 (16.1)	253 (13.7)	–0.067
Age, mean (SD), y	54.5 (10.9)	55.8 (11.0)	0.086
Male, n (%)	985 (53.1)	1056 (57.3)	0.159
Illiterate, n (%)	635 (34.5)	772 (41.9)	–0.056
Primary education, n (%)	374 (20.3)	331 (18.0)	–0.112
Secondary education and above, n (%)	847 (45.6)	739 (40.1)	–0.358
Employed, n (%)	647 (34.9)	354 (19.2)	–0.052
Previous ischemic heart disease, n (%)	66 (3.6)	49 (2.7)	–0.274
Previous peripheral vascular disease, n (%)	81 (4.4)	5 (0.3)	–0.003
Previous stroke, n (%)	33 (1.8)	32 (1.7)	–0.174
Previous cardiovascular disease, n (%)*	161 (8.7)	81 (4.4)	–0.219
Current tobacco user, n (%)	325 (17.5)	184 (10.0)	–0.152
Current alcohol user, n (%)	229 (12.3)	143 (7.8)	0.222
Physically inactive, n (%)	743 (40.0)	1113 (60.4)	0.122
Height, mean (SD), cm	159.0 (9.3)	157.7 (9.1)	–0.137
Weight, mean (SD), kg	65.4 (12.3)	64.6 (13.1)	–0.059
Body mass index, mean (SD), kg/m^2	25.8 (4.6)	26.0 (4.7)	0.031
SBP, mean (SD), mm Hg†	157.0 (16.3)	152.5 (14.7)	–0.238
Diastolic blood pressure, mean (SD), mm Hg†	93.3 (10.0)	88.8 (10.8)	–0.331
Fasting blood glucose, mean (SD), mg/dL‡§	197.7 (67.0)	185.9 (60.5)	–0.21
HbA_{1c}, mean (SD), %‡	9.3 (2.4)	9.5 (2.2)	0.049
Total cholesterol, mean (SD), mg/dL	191.8 (44.8)	194.5 (45.0)	0.061
CVD risk score, mean (SD), %	41.0 (21.9)	38.5 (20.2)	–0.120

CVD indicates cardiovascular disease; EUC, enhanced usual care; HbA_{1c}, glycated hemoglobin; SBP, systolic blood pressure; and SMD, standardized mean difference.

*Previous ischemic heart disease, peripheral vascular disease, and stroke combined.

†Participants with hypertension, n=2390 (EUC arm, 1231; mWellcare arm, 1159).

‡Participants with diabetes mellitus, n=1860 (EUC arm, 924; mWellcare arm, 936).

§Using capillary blood.

studying interactions allows a separate model per stratum and does not need to force the same regression to the mean effect or random-effects distribution in all strata.

RESULTS

Of the 4270 participants screened, 4056 met study eligibility criteria, and 3698 (EUC arm, 1856; mWellcare arm, 1842) were enrolled in the trial. Nearly 90% of the participants (n=3324) completed the end-of-study assessment at 12 months of enrollment (Figure 1).

Baseline Characteristics

Overall, at baseline, participants' mean age was 55.1±11.0 years, 55.2% were male, 42.9% had higher than primary school education, and 27.1% were employed. Table 1 shows baseline characteristics of participants by each arm. The EUC arm had a higher proportion of participants with secondary education and above (45.6% versus 40.1%), employment (34.9% versus 19.2%), peripheral vascular disease (4.4% versus 0.3%), self-reported tobacco use (17.5% versus 10.0%) and alcohol use (12.3% versus 7.8%), and higher mean SBP (157.0 mm Hg versus 152.5 mm Hg). Other baseline characteristics between the 2 arms were similar.

Table 2. End-of-Study Characteristics of Study Participants by Treatment Arm

Characteristics	EUC Arm	mWellcare Arm
Participants with baseline and end-of-study data, n	1687	1637
Age, mean (SD), y	55.5 (10.9)	56.7 (10.9)
Current tobacco user, n (%)	124 (7.4)	127 (7.8)
Current alcohol user, n (%)	114 (6.8)	120 (7.3)
Physically inactive, n (%)	1078 (63.9)	937 (57.2)
Height, mean (SD), cm	159.0 (9.3)	157.8 (9.1)
Weight, mean (SD), kg	65.6 (11.9)	65.1 (12.2)
Body mass index, mean (SD), kg/m^2	26.0 (4.6)	26.2 (4.6)
SBP, mean (SD), mm Hg*	138.6 (17.0)	136.6 (18.4)
Diastolic blood pressure, mean (SD), mm Hg*	83.8 (10.9)	82.3 (11.4)
Fasting blood glucose, mean (SD), mg/dL†‡	148.7 (67.9)	150.9 (66.8)
HbA_{1c}, mean (SD), %†	7.5 (2.4)	7.6 (2.3)
Total cholesterol, mean (SD), mg/dL	194.7 (45.2)	193.8 (45.2)
CVD risk score, mean (SD), %	41.5 (21.5)	41.0 (21.1)

CVD indicates cardiovascular disease; EUC, enhanced usual care; HbA_{1c}, glycated hemoglobin; and SBP, systolic blood pressure.

*Participants with hypertension.

†Participants with diabetes mellitus.

‡Using capillary blood.

Primary and Secondary Outcomes

Of the 3698 participants, 3324 (89.9%) completed the study assessment. We observed a significant decline in SBP from baseline to study end in each arm (EUC, −12.7 mm Hg; mWellcare, −13.7 mm Hg). Similarly, a significant decline in HbA_{1c} at 1 year was observed in both arms (EUC, −0.58%; mWellcare, −0.48%). However, we found no difference in change in SBP between the 2 arms (−1.0; 95% CI, −4.6 to 2.7), which were similar after adjustments (−0.3; 95% CI, −3.9 to 3.3). Similarly, there was no difference in the change in HbA_{1c} between the 2 arms (unadjusted, 0.11 [95% CI, −0.24 to 0.45]; after adjustments, 0.08 [95% CI, −0.27 to 0.44]). Table 2 gives the participants' characteristics at study end in the 2 arms, and Table 3 shows the difference in mean change from baseline to 1 year in the primary and secondary outcomes between the 2 arms, both unadjusted and adjusted for cluster and other variables that influenced the outcome measures.

The sensitivity analysis performed by imputing missing values for outcome variables revealed similar results (Table II in the online-only Data Supplement). The observed intraclass correlation coefficient in the data for the change of SBP was marginally higher than what we assumed for sample size calculation (assumed, 5% versus observed, 6%) but much lower for the change of HbA_{1c} (assumed, 4% versus observed, 2%). However, the power for the SBP analysis remained >97% with the current sample size.

There were no differences in secondary outcomes: fasting blood glucose, total cholesterol, predicted 10-year risk of CVD, body mass index, and tobacco and alcohol use. The difference in the mean score for alcohol use and the mean depression score, which was assessed only at the end of the trial, did not differ between the 2 arms.

Subgroup Analysis

Figures 2 and 3 depict results of subgroup analyses for the primary outcomes of SBP and HbA_{1c}, respectively, by state (Haryana and Karnataka), type of appointment of NCD nurse (trial fund supported versus NPCDCS supported), stage of hypertension (stage 1 versus 2), and metabolic profile at baseline, age, sex, education, and alcohol use. We did not observe any heterogeneity in the differences between the 2 arms.

Process Outcomes

Among key process indicators, adherence to medication (during the last 7 days) by participants showed a significant difference between arms (Table 4). Compared with the EUC arm, patients in the mWellcare arm reported greater adherence to antihypertensive

Table 3. Primary and Secondary Outcomes at the End of Study

Variable	Mean Change		Unadjusted		Adjusted*	
	EUC Arm	mWellcare Arm	Effect Size (95% CI)	*P* Value	Effect Size (95% CI)	*P* Value
Primary outcomes						
Change in SBP, mm Hg†	−12.7	−13.7	−1.0 (−4.6 to 2.7)	0.607	−0.3 (−3.9 to 3.3)	0.869
Change in HbA_{1c}, %‡	−0.58	−0.48	0.11 (−0.24 to 0.45)	0.563	0.08 (−0.27 to 0.44)	0.660
Secondary outcomes						
Fasting blood glucose, mg/dL‡§	−22.7	−15.0	7.7 (−10.3 to 25.6)	0.416	8.4 (−9.6 to 26.5)	0.372
Total cholesterol, mg/dL‖	2.0	0.1	−1.8 (−6.3 to 2.7)	0.444	−2.5 (−7.1 to 2.0)	0.292
CVD risk score, %‖	0.6	2.4	1.7 (−0.8 to 4.3)	0.196	−0.4 (−2.3 to 1.5)	0.658
Body mass index, kg/m^2‖	0.08	0.16	0.07 (−0.37 to 0.52)	0.749	−0.05 (−0.47 to 0.37)	0.823
Change in tobacco use, %‖	−7.0	−6.0	0.9 (−3.2 to 5.0)	0.649	−0.8 (−5.7 to 4.2)	0.756
Change in alcohol use, %‖	−3.8	−2.4	1.4 (−2.6 to 5.4)	0.480	0.7 (−3.7 to 5.1)	0.741
Variables assessed only at end of study						
Alcohol use score‖	10.0	9.4	−0.6 (−3.3 to 2.0)	0.642	−0.6 (−3.2 to 2.1)	0.683
Depression score‖	12.4	10.9	−1.4 (−4.2 to 1.4)	0.335	−1.6 (−4.4 to 1.2)	0.276

CVD indicates cardiovascular disease; HbA_{1c}, glycated hemoglobin; and SBP, systolic blood pressure.

*For SBP, we adjusted for education, lipid-lowering drugs, aspirin use, peripheral vascular disease, and smoking status; for HbA_{1c}, we adjusted for age, employed, antihyperglycemic drugs, peripheral vascular disease, and alcohol use; for fasting blood glucose, we adjusted for diabetes medication and peripheral vascular disease; total cholesterol was adjusted by height, employment, blood pressure medication, smoking, alcohol drinking and physical activity; for risk score, we adjusted for age, employment, blood pressure medication and smoking; for BMI, we adjusted for height, sex, marital status, education, employment, blood pressure medication, diabetes medication, lipid lowering medication, physical activity, smoking and alcohol; for change in tobacco and alcohol use, we adjusted for their own baseline values, age, sex, marital status, education and employment; for alcohol use and depression scores, we adjusted for age, sex, baseline alcohol and education.

†n indicates participants with hypertension.

‡n indicates participants with diabetes mellitus.

§Using capillary blood.

‖n indicates all participants.

(57.9% versus 81.1%) and antihyperglycemic (68.9 versus 82.4%) medications. During the trial period, there was no difference in drug availability between the arms. Among antihypertensive drugs, β-blockers and calcium channel blockers were more frequently available than angiotensin-converting enzyme inhibitors/angiotensin receptor blockers or diuretics. Among antihyperglycemic drugs, metformin was available 78.2% and 82.9% of the time whereas sulfonylureas were available only 42.9% and 45.6% of the time in the mWellcare and EUC arms, respectively. Overall, a high proportion of physicians accepted DSR prompts for hypertension and diabetes mellitus (68% and 69%, respectively). The most common cause for nonacceptance of the DSR was nonavailability of the EDS-recommended drugs at the CHC. Participants overwhelmingly noted improvement in the quality of care in both EUC and mWellcare CHCs (96.6% and 95.0%, respectively).

DISCUSSION

This cluster-randomized trial using hypertension and diabetes mellitus as entry points evaluated the effectiveness of mWellcare, an mHealth-based EDS, in the integrated management of hypertension and diabetes mellitus with comorbid conditions (depression and tobacco and alcohol use) in 40 CHCs in India for 12 months. The trial did not find any statistically significant difference in the prespecified primary outcomes of reduction in SBP or HbA_{1c} between the 2 arms. Secondary outcomes such as fasting blood glucose, total cholesterol, predicted 10-year risk of CVD, body mass index, depression, and tobacco and alcohol use were also not significantly different between the 2 arms. The primary outcome results were consistent across prespecified individual- and CHC-level subgroups despite heterogeneity among CHCs. This heterogeneity was potentially driven by site-level personnel (NPCDCS-appointed NCD nurses versus trial fund–supported NCD nurses), intervention fidelity, recruitment bias, or chance and requires future research. These results were also consistent in the sensitivity analyses.

Previous cluster-randomized trials in India evaluating EDS-based hypertension management in primary care demonstrated substantial reductions in SBP and better adherence to therapy, accompanied by significant improvement in lifestyle factors such as salt reduction, increased physical activity, and higher intake of fruits and vegetables.[15] The trial by Anchala et al,[15] however, focused on isolated hypertension management and was delivered entirely by physicians. Furthermore, the absence of nurse support in the control arm in this trial, compared with our study, may have resulted in the

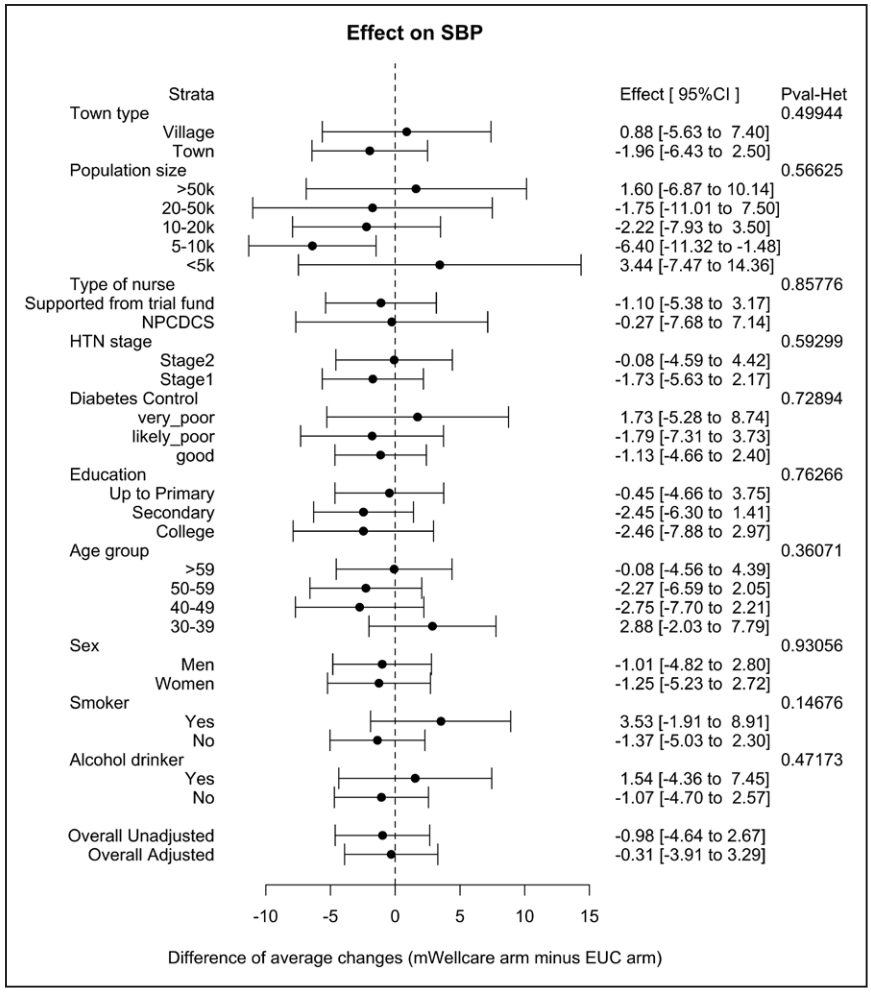

Figure 2. Primary outcome: systolic blood pressure (SBP) by prespecified baseline subgroups.
HTN indicates hypertension; NPCDCS, National Program for the Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke; and Pval-Het, *P* value–heterogeneity.

observed large difference between the 2 arms. Several systematic reviews and meta-analyses on the effectiveness of EDS report inconsistent and variable results (weak to modest positive results) for mean change in CVD risk factors such as SBP and diastolic blood pressure, total and low-density lipoprotein cholesterol, and HbA_{1c}.[12,13,34–36]

Several factors at the health system, care provider, and patient levels may have influenced the trial null results such as variations in the health system. These include infrastructural resources; leadership by the medical officer in charge; competing demands on the healthcare provider (the wide spectrum of diseases handled by a single CHC physician); NCD nurses assigned to do other duties, including immunizations and emergencies; and patient-level barriers (poor follow-up rates). Major factors that might have influenced the trial null results are described next.

First, the presence of NCD nurses in both the EUC and mWellcare arms could have influenced the results. NCD nurses in the EUC arm proactively maintained a separate register for the trial patients and provided special attention to trial participants in terms of scheduling follow-up visits and counseling on self-management, adherence to medications, and regular monitoring of blood pressure and glucose levels. This is reflected in the marked improvement in the quality of care reported in the EUC arm as in the mWellcare arm. A large trial from India (the CARRS trial) demonstrated a beneficial role of a nonphysician care coordinator enabled by EDS at tertiary care centers in improving the composite of HbA_{1c}, blood pressure, and low-density lipoprotein cholesterol. In contrast to our trial, the CARRS trial did not have a separate nonphysician care coordinator in the control group.[14] Second, the centralized training provided to the physicians and NCD nurses on hypertension and diabetes mellitus management could have improved the knowledge of care providers, translating to better quality of care in both arms, and diluted the benefit of EDS. Third, charts on treatment algorithms were also provided in clinics for physicians in the EUC arm, which could have influenced the findings. Fourth, the research team advocated for the availability of essential drugs for hypertension and diabetes mellitus management in all the participating CHCs, which is otherwise poor and inconsistently available.[16] The fortnightly visit by trial monitors for the process data collection, particularly drug availability, may have influ-

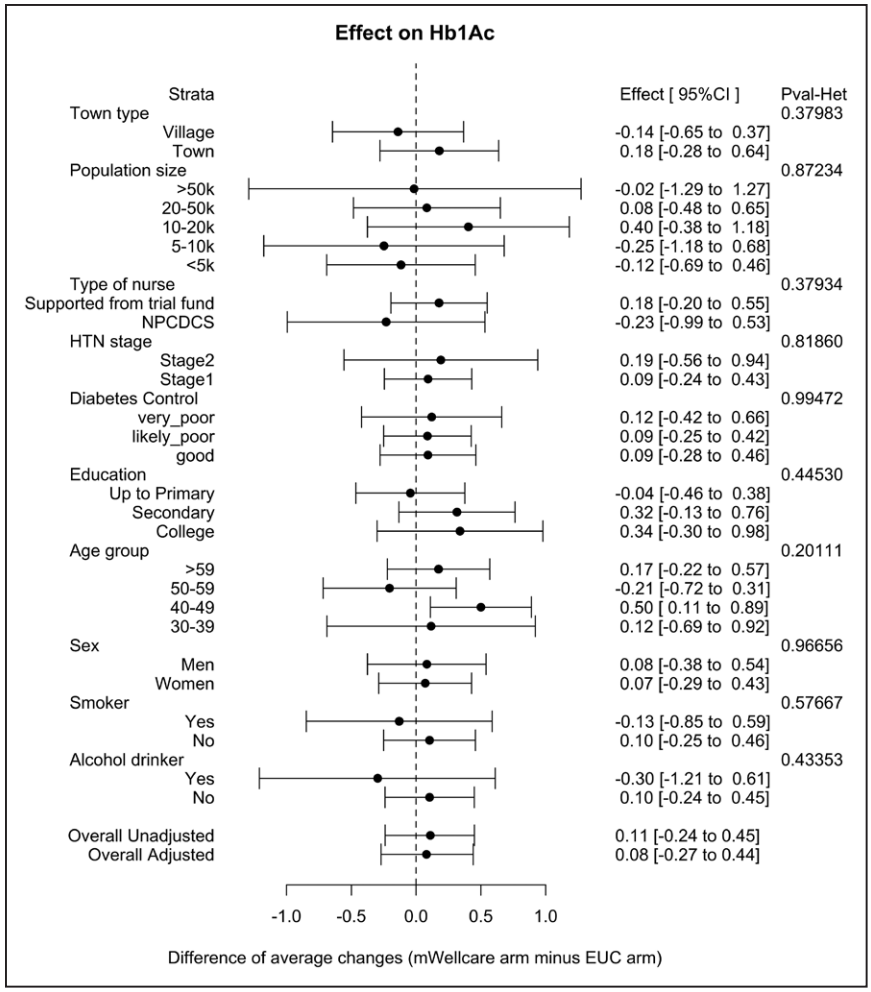

Figure 3. Primary outcome: glycohemoglobin (HbA_{1c}) by prespecified baseline subgroups.
HTN indicates hypertension; NPCDCS, National Program for the Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke; and Pval-Het, *P* value–heterogeneity.

enced the behavior of staff in ensuring the availability of drugs in the CHCs in both arms. Fifth, the Hawthorne effect, that is, behavioral change among care providers resulting from the open-label nature of the cluster-randomized trial, could have influenced better care delivery in the EUC arm, leading to null results. Process evaluation has documented that both arms had improvement in care delivery, drug availability, perceived quality of care by patients, and satisfaction of physicians in getting assistance from NCD nurses. Lastly, the mWellcare arm, compared with the EUC arm, had higher self-reported adherence to medication that did not translate into clinical benefits. Potential bias in self-reporting may have played a role; however, an absence of clinical benefit despite higher medication adherence has been observed in similar trials.[37,38]

Implications of Study Findings on India's National NCD Control Program

Although we found a null result, the trial demonstrated large reductions in blood pressure and HbA_{1c} in both arms. The reductions in blood pressure levels in both arms were comparable with the mPower Heart study, a pre-post evaluation of EDS-facilitated nurse-delivered intervention in Himachal Pradesh.[16] The role of nurses in the NCD clinics and the availability of drugs appear to have played crucial roles in improving outcomes. Furthermore, the trial facilitated a systematic patient assessment and guideline-based management and follow-up of patients with hypertension and diabetes mellitus. In addition, the training of physicians and NCD nurses (which is not otherwise part of usual care in India) may have contributed to the better quality of care. The government of India recently launched the ambitious Ayushman Bharat program, which aims to create 150 000 health and wellness centers to provide comprehensive primary health care, with a strong focus on prevention and management of NCDs through the provision of screening, follow-up, essential drugs, and diagnostic services facilitated by nonphysician care providers.[39] Thus, this trial supports the approach of the national program in terms of making provision for an NCD nurse for optimal management of chronic conditions. Additional components that need to be emphasized are the training of physicians and NCD nurses and ensuring a continuous and adequate drug supply. This trial also demonstrated the feasibility of incorporating

Table 4. Process Indicators

Process Indicators	EUC Arm	mWellcare Arm
Drug adherence during last 7 d		
Antihypertensive drug, all 7 d, n (%)	648 (57.9)	833 (81.1)
Antihyperglycemic drug, all 7 d, n (%)	570 (68.9)	683 (82.4)
Drug availability at CHCs, %*		
Antihypertensive drugs, %		
ACE inhibitor	53.8	52.4
ARB	51.2	56.2
BB	93.2	92.9
CCB	91.5	93.8
Diuretic	23.5	31.8
Antihyperglycemic drugs, %		
Metformin	82.9	78.2
Sulfonylurea	42.9	45.6
Aspirin	46.5	51.2
Statins	66.2	83.5
Participants' feedback on change in quality of care (n=1687, 1637 for EUC and mWellcare arms, respectively), %†		
Slightly/much better	95.0	96.6
About the same	4.4	3.3
Somewhat/much worse	0.5	0.2
Follow-up visit by the patients (n=1842), n (%)‡		
At least 1 follow-up visit in 12 mo, n (%)	…	1600 (86.9)
At least 4 follow-up visits in 12 mo, n (%)	…	876 (47.6)
Median follow-up visits, n	…	3.0
Acceptance rate of DSR by the physician, %‡		
Agreement with hypertension prompt	…	68
Agreement with diabetes mellitus prompt	…	69

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BB, β-blocker; CCB, calcium channel blocker; CHC, community health center; and DSR, decision support recommendation.

*Data collected fortnightly on availability of common drugs at each CHC at the given time point.

†Quality of care is the composite of the participant's perception of medicine availability, guidance from physicians, quality of care, frequency of blood pressure measurement, and care provided by the noncommunicable diseases nurse.

‡Follow-up data and acceptance of DSR were collected with the mWellcare application only in the mWellcare arm.

EDS and electronic storage of health records for NCD management in primary care. The government of India is preparing to roll out an electronic health record system in the public health system. This study can inform policymakers while that countrywide program is rolled out in India.

Strengths and Limitations

A major strength of this trial is that it tested an integrated strategy of managing 5 common chronic conditions with hypertension and diabetes mellitus used as entry points in a well-designed cluster-randomized controlled trial with adequate power. As far as possible, the trial mimicked a typical primary care healthcare system in India. Several system-level improvements were mandated as part of the trial, and robust process outcomes were carried out. Sophisticated statistical analysis to account for regression to the mean was performed.

Although this trial had null results, we demonstrated other benefits of using an mHealth system for NCD management. These benefits include generating an electronic patient registry, monitoring quality of care, centrally updating clinical protocols for all users through the mHealth application, and generating useful information from the registry for planning (eg, forecasting requirement of drugs, diagnostics, manpower).

However, we recognize some relevant limitations. Because of the trial's cluster design, we were unable to blind the healthcare team and participants. Furthermore, it was difficult to blind independent assessors who carried out the end-of-study evaluations. In addition, the enhancements in the EUC arm to make it comparable to the mWellcare arm could have affected the effect size substantially. Many cluster-randomized trials evaluating system-level quality interventions for CVD care have shown mostly null results.[40,41] A major reason for this outcome has been lack of power; however, our study had adequate power, and thus, the null result is truly informative.

Conclusions

We did not find an incremental benefit of mWellcare over EUC in the management of the chronic conditions studied. However, this study has important lessons for health systems in terms of the management of NCDs in primary care settings. The most important lessons are providing a clinic nurse to support the physician in the management of hypertension and diabetes mellitus, ensuring continuous availability of essential drugs, and periodic training of healthcare professionals on guideline-directed care.

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Correspondence

Dorairaj Prabhakaran, MD, DM, MSc, Public Health Foundation of India, 6th Floor, Plot 47, Sector 44, Gurugram (Haryana), 122 002, India. Email dprabhakaran@phfi.org

Affiliations

Centre for Control of Chronic Conditions, Public Health Foundation of India, Gurugram, India (D.P., K.S., D.K., S.G., V.P.). Centre for Chronic Disease Control, New Delhi, India (D.P., D.J., V.S.A., D.J., P.G., S.G.). London School of Hygiene & Tropical Medicine, UK (D.P., D.P.-M., P.P.). Applied Statistical Methods in Medical Research Group, Universidad Católica San Antonio de Murcia, Spain (D.P.-M.). All India Institute of Medical Sciences, New Delhi (A.R.). dWise IT Solutions, Bangalore, India (P.J.). Directorate of Health Services, Government of

Haryana, Panchkula, India (R.S.). Directorate of Health and Family Welfare Services, Government of Karnataka, Bengalore, India (B.G.P.K.). Centre for Control of Chronic Conditions, All India Institute of Medical Science, New Delhi (N.T.). Department of Global Health and Social Medicine, Harvard Medical School, Boston, MA (V.P.). Department of Global Health and Population, Harvard TH Chan School of Public Health, Boston, MA (V.P.). Sangath, Goa, India (V.P.).

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Disclosures

Drs Prabhakaran, Tandon, Roy, Vamadevan, and Jindal hold a copyright for the mPower Heart mHealth System, which has features on electronic storage of health records and electronic clinical decision support computation. They had/have been doing research projects implementing and evaluating EDS systems in multiple settings. Dr Prabhakaran is partially supported through research grants from the National Institutes of Health (grants 5U01TW01009702, 5U2RTW01010804, 5R01HL12544204, 5R21DK10589102, and 5P20CA21029802). Dr Tandon is the principal investigator for an investigator-initiated research grant from the National Institutes of Health (grant 5U01HL13863502). Dr Goenka was supported by Bernard Lown Scholars in Cardiovascular Health Program, Harvard School of Public Health (2015–2017), and Wellcome Trust (grant 203124/Z/16/Z) 2018. The other authors report no conflicts.

APPENDIX

Members of the Research Steering Committee: Prof D. Prabhakaran,* Vice President, Centre for Control of Chronic Conditions, Public Health Foundation of India, Gurugram, India; Prof Vikram Patel,* Pershing Square Professor of Global Health, Department of Global Health and Social Medicine, Harvard Medical School, Boston, MA; Prof Nikhil Tandon,* Professor and Head, Department of Endocrinology, All India Institute of Medical Sciences, New Delhi, India; Prof Ambuj Roy,* Professor, Department of Cardiology, All India Institute of Medical Sciences, New Delhi, India; Prof Pablo Perel,* Professor of Clinical Epidemiology, Centre for Global Chronic Conditions, London School of Hygiene & Tropical Medicine, London, UK; Dr C. Venkat S. Ram, Director, Apollo Institute of Blood Pressure Management, Hyderabad, India; Sudhir Saxena, Vice President, National Institute for Smart Government, New Delhi, India; Prof K. Venugopal, Professor of Cardiology, Amrita Institute of Medical Sciences, Kochi, India; Dr Lars Gredsted, Senior Business Analyst, Wellcome Trust, London, UK; Dr Vikram Sheel Kumar, Founder and Chief Medical Officer, Dimagi Inc, Cambridge, MA; Dr Shirshendu Mukherjee, Mission Director, Programme Management Unit, Biotechnology Industry Research Assistance Council, New Delhi, India; Dr Rekha Singh,* Deputy Director (NCD), Directorate of Health Services, Government of Haryana, Panchkula, India; and Dr B.G. Prakash Kumar,* Deputy Director (NCD), Department of Health & Family Welfare Services, Government of Karnataka, Bangalore, India. Investigators: Prof D. Prabhakaran, Vice President, Centre for Control of Chronic Conditions, Public Health Foundation of India, Gurugram, India; Prof Pablo Perel,* Professor of Clinical Epidemiology, Centre for Global Chronic Conditions, London School of Hygiene & Tropical Medicine, London, UK; Prof Vikram Patel,* Pershing Square Professor of Global Health, Department of Global Health and Social Medicine, Harvard Medical School, Boston, MA; Prof K. Srinath Reddy,* President, Public Health Foundation of India, Gurugram, India; Prof Nikhil Tandon,* Professor and Head, Department of Endocrinology, All India Institute of Medical Sciences, New Delhi, India; and Prof Ambuj Roy,* Professor, Department of Cardiology, All India Institute of Medical Sciences, New Delhi, India. Members of the Data Safety and Monitoring Board: Prof Nitish Naik (chair), Professor, Department of Cardiology, All India Institute of Medical Sciences, New Delhi, India; Prof S.N. Dwivedi, Professor, Department of Biostatistics, All India Institute of Medical Sciences, New Delhi, India; Dr A.G. Unnikrishnan, Endocrinologist and Chief Executive Officer, Chellaram Diabetes Institute, Pune, India; and Dr Meenakshi Sharma, Scientist F, Indian Council of Medical Research, New Delhi, India.
*Wrote the manuscript.

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