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A community health worker-led intervention decreases glycated haemoglobin and systolic blood pressure in rural Mexico

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ABSTRACT

Objectives: Community health workers (CHWs) can support primary healthcare systems, but there is a lack of data on their effectiveness in managing noncommunicable diseases (NCDs) in low- and middle-income countries (LMICs). The aim of this study was to determine whether a CHW-led intervention targeting diabetes and hypertension could improve markers of clinical disease control in rural Mexico.

Design and setting: A prospective observational study was conducted across seven communities/primary health centres in rural Chiapas, Mexico from March 2014 to April 2018.

Participants: We analyzed 149 adults with hypertension and/or diabetes.

Intervention: This study was conducted in the context of the programmatic roll-out of a CHW-led intervention designed to complement comprehensive primary care for adults with diabetes and/or hypertension. Implementation occurred sequentially at three-month intervals with point-of-care data collected at baseline and every three months thereafter for 12 months following roll-out in all communities.

Outcome measures: Primary outcomes were glycated haemoglobin (HbA1c) and systolic blood pressure. We conducted an individual-level stepped-wedge analysis using mixed effects regression, and adjusting for time, cohort, and clustering at the individual and community levels.

Results: In adjusted analyses, the CHW-led intervention was associated with a -0.3% difference in HbA1c (95% CI -0.9 to 0.3%) among patients with diabetes and a -5 mm Hg difference in systolic blood pressure (95% CI -9 to -1 mm Hg) in patients with hypertension. In diabetic patients with HbA1c ≥ 9%, the decrease in HbA1c was 0.9% (95% CI -1.7 to -0.2%), and in patients with uncontrolled hypertension systolic blood pressure decrease was 10 mm Hg (95% CI -18 to -3 mm Hg). The intervention was also positively associated with disease control in patients with hypertension.

Conclusions: The CHW intervention led to clinically meaningful improvement in disease markers for patients with diabetes and hypertension, supporting a valuable role for CHWs in supporting NCD management in rural LMICs.

Trial registration: NCT02549495

STRENGTHS AND LIMITATIONS

- This study provides the first prospective evaluation of a CHW-led intervention, versus comprehensive primary care alone, on measures of clinical disease control among patients with NCDs in Latin America.
- We expand on a prior analysis to quantify the effect of the CHW intervention on clinical indicators of diabetes and hypertension control in an expanded cohort of communities and patients, examining whether the intervention performed differently in patients with poor disease control.
- Utilizing the programmatic stepped roll-out of the CHW intervention allowed for individual-level analysis as in a stepped-wedge trial, limiting confounding by stable individual-level characteristics.
- The stepped wedge design is a practical approach for implementation and evaluation of low-risk interventions expected to confer a large benefit in impoverished settings, limiting the ethical issue of nontreatment common to randomised trials.
- Limitations of this study include small sample size and evaluation in a single rural, remote region, though the successes of the intervention in spite of numerous barriers suggest that the findings may be generalisable to other remote, rural settings

INTRODUCTION

In 2012, over two-thirds (38 million) of all deaths worldwide were attributable to noncommunicable diseases (NCDs) including cardiovascular disease and diabetes. Nearly three-quarters (28 million) of these occurred in low- and middle-income countries (LMICs).[1] Poor patients suffer a higher burden of NCD risk factors and worse outcomes.[2]

Community Health Workers (CHWs) have the potential to play a significant role in strengthening health systems worldwide, with increasing interest in their support for NCD management.[3] Understanding the effect of CHW interventions on biologic markers of disease control is important because these markers help anticipate the effects of successful programs on individual and population health. In patients with diabetes, a 1% decrease in glycated haemoglobin (HbA1c) has been associated with a 1% reduction in diabetes-related deaths, 14% reduction in myocardial infarction, and 37% decrease in microvascular complications.[4] A meta-analysis of prospective trials of blood pressure-lowering medications documented a 22% reduction in coronary heart disease events and 41% reduction in stroke for a blood pressure reduction of 10 mm Hg systolic or 5 mm Hg diastolic.[5]

Most high-quality evidence supporting the role of CHWs in NCD control comes from high-income countries including the United States. Systematic reviews of CHW-led interventions in patients with diabetes and hypertension demonstrated improvements in HbA1c and systolic blood pressure, respectively, across multiple randomised controlled trials.[6,7] However, differences in patients, health infrastructure, and CHW roles make it difficult to generalise these results to LMIC and rural settings.

Evidence for the ability of CHWs to improve NCD control in LMICs is varied. Two recent systematic reviews examined the evidence for CHWs in LMICs in the prevention, identification, and management of diabetes and cardiovascular disease. While highlighting positive outcomes in a majority of studies, both identified significant heterogeneity among designs of CHW interventions and limitations due to study design, high rates of attrition, absence of detailed reporting on operational design, inappropriate statistical analysis, and variable program fidelity.[8,9] Among patients with diabetes, two studies of CHW-led interventions demonstrated improvement in fasting plasma glucose (with more modest results among patients with hypertension).[10,11] Additional retrospective studies and cluster-randomised trials in patients with hypertension demonstrated an association with better blood pressure control.[12-15] However, the randomised trials were limited in their ability to separate the impact of the CHW-led intervention from multicomponent programs adding clinic-level supports.[14,15]

In Mexico, between 2010 and 2012, diabetes and ischaemic heart disease were the two leading causes of mortality.[16] A 2016 national survey estimated that 9·4% and 26% of Mexican adults had diabetes and hypertension, respectively,[17] with low rates of clinical control and increasing prevalence across most demographics.[16-18] The Mexican Ministry of Health (MOH) identifies NCDs and corresponding risk factors as a priority and recognizes the need for scalable, evidence-based interventions that address promotion of healthy behaviours and disease management.[18] While there is no national-level CHW programme in Mexico, national strategies emphasise active community participation in addressing the rising burden of NCDs, advocate for the creation of community committees, and encourage partnership with non-governmental organisations.[16,18] Experience using Mexican *Promotores de Salud* as CHWs focused on education and lifestyle modification has been varied but promising,[19] though they have not yet been widely mobilised to provide individual or instrumental support in NCD management. Compañeros en Salud (CES) is an affiliate of the multinational non-governmental organization Partners in Health. CES works in collaboration with the Mexican Ministry of Health in Chiapas, Mexico, a state with the highest rates of poverty and extreme poverty and one of the lowest rates of effective health coverage in the country.[20] We previously found that a CHW intervention led to improved medication adherence and disease control among patients with diabetes and hypertension.[21] Here we expand on this prior analysis to quantify the effect of the intervention on clinical indicators of diabetes and hypertension control in an expanded cohort of communities and patients, examining whether the intervention performed differently in patients with poor disease control. We hypothesized that the intervention would reduce HbA1c in patients with diabetes and systolic blood pressure in patients with hypertension.

METHODS

Study Design

This study was structured around the planned programmatic roll-out of a CHW intervention targeting diabetes and hypertension in seven rural, remote communities (population 1000 - 2500) in Chiapas, Mexico where CES operates. To ensure sufficient time for implementation, including training and supervision of CHWs, the intervention was sequentially implemented at three-month intervals. The first cohort included four communities in which CES had been working for two years. Study enrollment took place during March 2014 with intervention implementation at three month intervals and data collection through January 2016 (figure 1), and we found improved disease control and medication adherence among all patients.[21] However, due to the small sample, the analysis combined patients with diabetes and hypertension and we were unable to quantify the disease-specific clinical effects of the intervention. Based on these findings, the intervention was subsequently scaled to three additional communities in which CES had been supporting primary care for two years. Enrollment took place during July 2016, with implementation and data collection in this cohort through April 2018. In both cohorts, data collection took place at baseline (i.e. prior to implementation in any community) and every three months thereafter for 12 months following implementation of the intervention in all seven communities (figure 1).

This study was reviewed and approved by institutional review boards of the Brigham and Women's Hospital (Partners Human Research Committee) and the Instituto Tecnológico de Monterrey. Participants provided verbal informed consent, which was documented in writing by study staff.

Intervention

CES has partnered with the Mexican Ministry of Health since February 2012 to provide comprehensive primary care and management for patients with NCDs, in accordance with national guidelines. The care model includes monthly clinic visits and treatment with common oral medications for diabetes and hypertension, which are provided free-of-charge to patients. The CHW-led intervention follows a community-based accompaniment approach centered on regular home visits, previously demonstrated to be effective at improving disease outcomes and medication adherence in patients with HIV.[22,23] CHWs serve as a bridge between patient and clinic, promoting medication adherence, reinforcing basic disease education, providing psychosocial support, and supporting active case retention. The overall structure of the CHW-led intervention was the same in both cohorts.

Study Participants

Patients with diabetes, hypertension, and respective risk factors were identified via a CES program of clinic-based and door-to-door case finding. Each community has one health centre staffed by a social service general physician who maintains registries of patients with NCDs, which served as the basis for eligibility determination and recruitment. Eligible patients were those who had a diagnosis of diabetes and/or hypertension, were aged 18 years or older at the time of enrolment, resided in a study community, and were prescribed daily medications by the clinic physician for treatment of diabetes and/or hypertension. We excluded patients with secondary hypertension, type 1 diabetes, pregnancy, and chronic use of glucocorticoids. We also excluded patients who, after enrolment but prior to implementation of the intervention in the first community, were removed from treatment by their physician, moved outside the study community, transferred care to another health facility, or who were determined not to have a diagnosis of diabetes or hypertension.

Patient and Public Involvement

Patients and the public were not involved in the design, conduct, or reporting of this study.

Outcomes

The primary outcomes for this study were HbA1c and systolic blood pressure, analysed as continuous variables. These were analysed among all patients with diabetes and hypertension, respectively, and in subgroups characterized by level of disease control at baseline. Poor diabetes control at baseline was defined as HbA1c ≥ 9%,reflecting the standard of various quality metrics.[24] Disease control among patients with hypertension was defined according to Mexican national guidelines: blood pressure <140/90 mm Hg for patients with hypertension

and no diabetes; blood pressure <130/80 mm Hg for patients with hypertension and diabetes and blood pressure < 150/90 mm Hg for patients over the age of 80.[16] Secondary outcomes included diastolic blood pressure, analysed as a continuous variable, and disease control examined as a binary variable (i.e. HbA1c < 7% for diabetic patients per national guidelines and the above thresholds for hypertensive patients). The latter analyses were conducted overall (with disease control defined as control of both diabetes and hypertension if the patient had both diagnoses) and separately by disease.

Statistical methods and data analysis

The study size was determined by the number of patients meeting eligibility criteria in the communities where the intervention was to be implemented, so power calculations did not inform any sample size targets. Outcomes assessments for individuals who withdrew from the study for any reason were included until the time at which they withdrew. We conducted individual-level mixed effects analyses including random intercepts for each individual and community to adjust variances for individual repeated measures and clustering by community, respectively.[25,26] The random intercept for community was excluded from the model if the variance for the intercept was zero to avoid overfitting. We modeled continuous outcomes (HbA1c, systolic blood pressure, diastolic blood pressure) using linear mixed models with maximum likelihood estimation.[25] Binary outcomes were modeled using generalised linear mixed models with Laplace maximum likelihood estimation and a logit link.[25,27] Fixed effects included a binary variable to indicate whether the person lived in a community that was exposed to the intervention at a given time point, a categorical variable for time (i.e. corresponding to each intervention / data collection step) and an indicator variable for cohort (first versus second). We conducted stratified analyses to examine whether any effect of the intervention depended on baseline disease control and calculated p-values for differences in continuous outcomes and odds ratios (ORs) using Cochran's Q-test for heterogeneity. We conducted three sensitivity analyses; in the first, we assessed the primary and secondary outcomes using 2017 Mexican MOH guidelines for hypertension featuring more liberal blood pressure targets: <140/80 in patients with hypertension and diabetes, <150/90 if over the age of 60 with hypertension and without diabetes, and <140/90 if over the age of 60 with hypertension and diabetes.[28] In the second, we adjusted for community as a fixed effect; in the third, we excluded 11 patients who were removed from treatment by their providers during the study. Analyses were conducted using SAS V9·4 (Cary Institute, Cary, North Carolina). This study is registered at ClinicalTrials.gov (NCT02549495).

RESULTS

Description of the study cohort and data completeness

We screened 192 patients identified through clinic NCD registries and enrolled 168 patients who provided informed consent in March 2014 (cohort 1) and July 2016 (cohort 2; figure 2). 19 patients (11%) were excluded prior to intervention or analysis. Of the 149 patients analyzed, 39 (26%) had diabetes, 79 (53%) had hypertension, and 31 (21%) had both diseases. The average cluster size was 21 (SD 10). 127 patients (85%) contributed data through the completion of the study. Twenty-two patients withdrew from the study; in eleven, this was due to physician discontinuation of therapy. Of a total 1204 possible data collection time points corresponding to active study participation (i.e. excluding data collection that would have occurred following a withdrawal), we collected data at 1154 time points (96%). Of these, individuals at 397 time points were unexposed to the intervention and 757 were exposed.

Baseline demographic and disease data are presented in table 1. 64% of patients (n=96) were female with a median age of 58 years [IQR 50, 71]. The median HbA1c in patients with diabetes was 9.3 [IQR 7.2, 11.7] with 53% (n=37) having a HbA1c ≥ 9%. 22% of patients (n=15/69) with diabetes had disease control at baseline. The median systolic blood pressure in patients with hypertension was 135 [IQR 126, 151]. 59% of patients (n=61) with hypertension had disease control at baseline.

Table 1 Baseline characteristics of study participants (n=149) [a]

Community	Overall (n=149)	1 (n=43)	2 (n=24)	3 (n=25)	4 (n=16)	5 (n=16)	6 (n=11)	7 (n=14)
Male, n (%)	53 (36)	19 (44)	5 (21)	6 (24)	7 (44)	6 (38)	3 (27)	7 (50)
Median Age, years [IQR] (n=142)	58 [50, 71]	59 [54, 72]	54 [48, 70]	61 [54, 73]	55 [50, 71]	58 [52, 66]	61 [47, 69]	57 [46, 71]
Has a radio, n (%)	93 (62)	30 (70)	12 (50)	17 (68)	7 (44)	13 (81)	5 (45)	9 (64)
Has a car/ motorcycle, n (%)	43 (29)	8 (19)	6 (25)	11 (44)	4 (25)	3 (19)	5 (45)	6 (43)
Type of remuneration								
Salary, n (%)	8 (5)	1 (2)	0 (0)	1 (4)	4 (25)	0 (0)	0 (0)	2 (14)
Day Labor, n (%)	58 (39)	15 (35)	9 (38)	5 (20)	2 (13)	11 (69)	9 (82)	7 (50)
None, n (%)	83 (56)	27 (63)	15 (63)	19 (76)	10 (63)	5 (31)	2 (18)	5 (36)
Diabetes Diagnosis, n (%)	70 (47)	28 (65)	12 (50)	6 (24)	9 (56)	10 (63)	2 (18)	3 (21)
HbA1c (%), median [IQR]	9.3 [7.2, 11.7]	8.1 [7.1, 10.6]	11.7 [9.3, 13]	7.9 [7.8, 9.3]	11.3 [10.0, 13.0]	8.8 [7.0, 12.6]	8.1 [6.3, 9.9]	6.2 [5.1, 10.3]
HbA1c ≥ 9%, n (%)	37 (53)	11 (39)	9 (75)	2 (33)	8 (89)	5 (50)	1 (50)	1 (33)
Controlled Diabetes[b], n (%) (n=69)	15 (22)	7 (26)	1 (8)	1 (17)	0 (0)	3 (30)	1 (50)	2 (67)
Hypertension Diagnosis, n (%)	110 (74)	34 (79)	12 (50)	23 (92)	7 (44)	13 (81)	10 (91)	12 (86)
Systolic BP (mm Hg), median [IQR]	135 [126, 151]	130 [117, 146]	150 [125, 173]	135 [120, 145]	145 [132, 197]	146 [138, 151]	139 [144, 151]	132 [126, 138]
Diastolic BP (mm Hg), median [IQR]	80 [72, 88]	77 [69, 86]	84 [74, 93]	79 [72, 85]	89 [71, 105]	82 [79, 92]	86 [84, 91]	77 [73, 82]
Controlled Hypertension[c], n (%)	61 (59)	20 (59)	5 (42)	16 (73)	2 (29)	5 (38)	5 (50)	9 (75)
Controlled Diabetes / Hypertension[d], n (%) (n=148)	61 (41)	18 (43)	6 (25)	15 (60)	2 (13)	4 (25)	6 (55)	10 (71)

[a] Unless otherwise stated. [b] Defined as glycated haemoglobin (HbA1c) < 7%. [c] Defined as blood pressure (in mm Hg) < 140/90, <130/80 if concomitant diabetes, <150/90 if age ≥ 80 according to 2010/2014 Mexican Ministry of Health guidelines.[16] [d] Defined as control of diabetes if diagnosed with diabetes, hypertension if diagnosed with hypertension, or both if dual diagnosis.

Continuous Outcomes of HbA1c and Blood Pressure

In adjusted analysis, among 73 patients with diabetes, there was a 0.3% decrease in HbA1c (95% CI -0.9 to 0.3%, p=0.29) with exposure to the intervention (figure 3a). Among 117 patients with hypertension, there was a 5 mm Hg decrease in systolic blood pressure with exposure to the intervention (95% CI -9 to -1 mm Hg, p=0.03, figure 3b) and a 2 mm Hg decrease in diastolic blood pressure (95% CI -5 to 0 mm Hg, p=0.06).

In patients with diabetes with HbA1c ≥ 9% at baseline (n=37), relative to no intervention, exposure to the CHW intervention resulted in a 0.9% decrease in HbA1c (95% CI -1.7 to -0.2%, p=0.01, figure 3a). There was no evidence of a clinically significant intervention effect among patients with HbA1c < 9% at baseline (estimate 0.2%, 95% CI -0.5 to 0.9%, p=0.6, n=36).

In patients with uncontrolled hypertension at baseline (n=48), exposure to the intervention resulted in a -10 mm Hg adjusted difference in systolic blood pressure (95% CI -18 to -3 mm Hg, p=0.007, figure 3b) relative to no intervention. Among patients with baseline hypertension control (n=62), the intervention was associated with a reduction of 3 mm Hg (95% CI -7 to 2 mm Hg, p=0.23). Similar results were observed for diastolic blood pressure:

patients with uncontrolled baseline hypertension had a -5 mm Hg difference (95% CI -9 to -1 mm Hg, p=0.02) and patients with baseline control -1 mm Hg (95% CI -4 to 2 mm Hg, p=0.39).

Binary Outcomes of Controlled Diabetes and Hypertension

Relative to no intervention, receipt of the intervention was associated with a 2.5-fold increase in the odds of disease control among all participants (adjusted OR 2.50, 95% CI 1.26 to 4.99, p=0.009, n=149, table 2). When stratified by baseline disease control, there was a larger effect observed among patients without (adjusted OR 4.25, 95% CI 1.42 to 12.70, p=0.001, n=87) versus with (adjusted OR 2.32, 95% CI 0.84 to 6.39, p=0.1, n=61) disease control at baseline (p-value for interaction: 0.43).

In patients with diabetes, there was a 2.7-fold increase in odds of disease control (adjusted OR 2.69, 95% CI 0.72 to 10.14, p=0.14, n=73, table 2). Among all patients with hypertension, the intervention was associated with a 3.2-fold increase in the odds of disease control (adjusted OR 3.18, 95% CI 1.55 to 6.55, p=0.002, n=117).

Overall, we observed a greater effect of the intervention among patients with uncontrolled disease at baseline. The effect was larger among patients with uncontrolled diabetes at baseline (adjusted OR 5.35, 95% CI 0.89 to 32.17, p=0.07, n=54) as compared to baseline disease control (adjusted OR 1.46, 95% CI 0.06 to 37.26, p=0.82, n=15; p-value for interaction: 0.49). We also observed a greater effect among patients with uncontrolled hypertension at baseline (adjusted OR 6.28, 95% CI 1.79 to 22.06, p=0.004, n=48) than among patients with baseline controlled hypertension (adjusted OR 2.65, 95% CI 0.99 to 7.12, p=0.05, n=62; p-value for interaction: 0.29).

Table 2 Intervention effectiveness, stratified by disease and baseline disease control

	Adjusted OR (95% CI)	p-value	Interaction
All Patients (n=149 [1146])	2.50 (1.26 – 4.99)	0.009	
Not Controlled at Baseline (n=87 [664])	4.25 (1.42 - 12.70)	0.01	0.43
Controlled at Baseline[a] (n=61 [477])	2.32 (0.84 - 6.39)	0.10	
Diabetes (n=73 [543])	2.69 (0.72 - 10.14)	0.14	
Not Controlled at Baseline (n=54 [417])	5.35 (0.89 - 32.17)	0.07	0.49
Controlled at Baseline[b] (n=15 [109])	1.46 (0.06 - 37.26)	0.82	
Hypertension (n=117 [869])	3.18 (1.55 - 6.55)	0.002	
Not Controlled at Baseline (n=48 [364])	6.28 (1.79 - 22.06)	0.004	0.29
Controlled at Baseline[c] (n=62 [486])	2.65 (0.99 - 7.12)	0.05	

Individual-level mixed effects analysis adjusting for time and cohort and random intercepts to account for clustering by individual and community (n=number of individual patients [number of time points]). [a] Defined as control of diabetes if diagnosed with diabetes, hypertension if diagnosed with hypertension, or both if dual diagnosis. [b] Defined as glycated haemoglobin (HbA1c) < 7%. [c] Defined as blood pressure (in mm Hg) < 140/90, <130/80 if concomitant diabetes, <150/90 if age ≥ 80 according to 2010/2014 Mexican Ministry of Health guidelines.[16]

Sensitivity analysis

Analysis of the above outcomes using 2017 Mexican MOH blood pressure guidelines, adjusting for community as a fixed effect, or excluding 11 patients removed from treatment by their provider did not change the interpretation of the primary findings (online supplementary tables 1-3).

DISCUSSION

We found that a CHW-led intervention, when added to comprehensive primary care in rural Mexico, significantly improved markers of disease control, including HbA1c in patients with diabetes and systolic blood pressure in patients with hypertension. This study builds on our prior findings to demonstrate the isolated impact of a CHW-led

intervention on markers of NCD control versus primary care alone. To our knowledge, this is the first prospective study in Latin America to demonstrate this effect. Unlike prior studies in LMICs which reinforced the primary care delivery structure,[14,15] this program demonstrated significant improvements in markers of disease control when added to an already comprehensive structure of primary care. Our results are consistent with evidence from randomised trials in high income counties.[6,7]

Clinically, these effects are similar to those seen with adding additional medications to treatment regimens for patients with diabetes or hypertension.[5,29] As such, the clinical effects observed from CHWs represent a non-pharmacologic intervention that could significantly reduce diabetes- and hypertension-associated morbidity and mortality. By allocating healthcare financing to human-mediated inputs such as paying, training, and supporting CHWs in addition to medication supplies, there are ancillary benefits for society including empowerment of women, economic stimulation, and decreased unemployment. Any approach that aims to comprehensively address the social determinants of disease and improve outcomes will require new investments in order to build and finance truly functional health systems.

Methodologically, we addresses many limitations of the existing literature for CHWs targeting NCDs in LMICs in areas of study design, rate of attrition, and statistical analysis.[8,9] This study assessed the impact of the CHW-led intervention in the context of a programmatic stepped roll-out, allowing us to collect outcome data from patients at times when unexposed and exposed to the intervention, while accounting for underlying time trends. A key strength of this analysis is that we can rule out confounding by stable individual-level characteristics. The stepped wedge design is a practical approach for implementation and evaluation of low-risk interventions expected to confer a large benefit in impoverished settings, limiting the ethical issue of nontreatment common to randomised trials. This design, along with our sensitivity analyses, suggest a causal benefit of this CHW-led intervention on diabetes and hypertension outcomes.

It is important to note that this study was conducted in a population that included both controlled and uncontrolled patients. Although our results suggest a stronger effect among uncontrolled patients, our experience suggests that CHWs may learn and benefit from interactions with patients who are able to achieve clinical control. Additionally, disease control in NCDs like diabetes and hypertension can be dynamic, fluctuating over time for an individual patient and posing an increased risk of complications.[30] For these reasons, we advocate CHW interventions targeting all patients and, at minimum, the most socially vulnerable, not only those with the worst control.

We did not expect differences between cohorts, as CES had been working in the initial communities for the same amount of time at implementation as in the second cohort. Nonetheless, we accounted for potential effect modification by cohort in adjusted analysis. Although the sample size was small for drawing statistical comparisons across subgroups, the magnitude and direction of effect estimates were consistent, supporting a benefit of the CHW-led intervention across both diseases. We note that although our outcomes (HbA1c, blood pressure) remain surrogates for clinically meaningful disease-specific complications, the body of evidence supports their use in this association.[4,5] While this program was evaluated in a single rural, remote setting, the success of this intervention in spite of the barriers encountered, including limited phone and internet access, dirt roads, and long distances to higher levels of care, suggests that our findings may be generalisable to other remote, rural settings.

In conclusion, implementation of a prospective CHW-led intervention targeting NCDs in rural Mexico improved measures of disease in patients with diabetes and hypertension. Programmes and health systems aiming to improve care of patients with NCDs may consider this study as supportive evidence for the addition of CHWs to strengthen rural primary care systems in LMICs. In moving towards universal health coverage, CHWs may be as effective as additional medications in managing these NCDs and have great potential for further social impact.

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Contributors: DTW oversaw data collection, carried out the analysis, produced figures and tables, led the literature search, and drafted the manuscript. MF, HF, LP, PMN, and DP contributed to study design. JK and KR led data collection teams. DTW, RB, ZG, JM, and PMN oversaw the data collection process and ensured data quality. MF was the lead methodologist and designed the analysis. JK contributed to the literature search and manuscript preparation. PMN and DP are responsible for the original conceptualisation, study oversight, and critical review of the manuscript as principal investigators. All authors contributed to interpretation of the work, editing of the manuscript, and final approval of this version, and agree to be accountable for all aspects of the work.

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Provenance and peer review: Not commissioned; externally peer-reviewed.

Data sharing statement: De-identified primary data and a technical appendix are available on reasonable request from the authors.

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FIGURE LEGENDS

Figure 1 Stepped-wedge schematic for the study

Programmatic roll-out was randomised by community (cluster) with sequential implementation of the intervention resulting in each community contributing time as unexposed (purple) and exposed (peach) to the CHW-led intervention. Data were collected at the start of each 3-month time point across two cohorts regardless of whether the intervention had been implemented. In the first cohort (communities 1-4), data collection took place from March 2014 through January 2016. In the second cohort (communities 5-7), data collection took place from July 2016 through April 2018. Delays in baseline data collection in cohort 1 shortened the duration of period 1 from three months to one month. Organizational delay in roll-out for cohort 2 shortened the baseline pre-randomisation phase and resulted in a 3-month delay in implementation in community 7.

Figure 2 Flow of participants through the study

Figure 3 Diabetes and hypertension continuous outcomes

Adjusted mean difference between exposed and unexposed for glycated haemoglobin (HbA1c) among patients with diabetes (A) and average systolic blood pressure in patients with hypertension (B). Individual-level mixed effects analysis adjusting for time and cohort with clustering by individual and community presented as estimate (square) and 95% confidence intervals (lines). A. Diabetes outcomes among all patients (n=79 [543 timepoints]) and dichotomized between poorly controlled (HbA1c ≥ 9%, n=37 [278]) and not poorly controlled (HbA1c < 9%, n=36 [265]) at baseline. B. Hypertension outcomes among all patients (n=117 [869 time points] and dichotomized between not controlled (n=49 [364]) and controlled (blood pressure (in mm Hg) <140/90, <130/80 if concomitant diabetes, <150/90 if age ≥ 80 according to 2010/2014 Mexican Ministry of Health guidelines,[16] n=62 [486]) at baseline.

Figure 1 **Stepped-wedge schematic for the study**

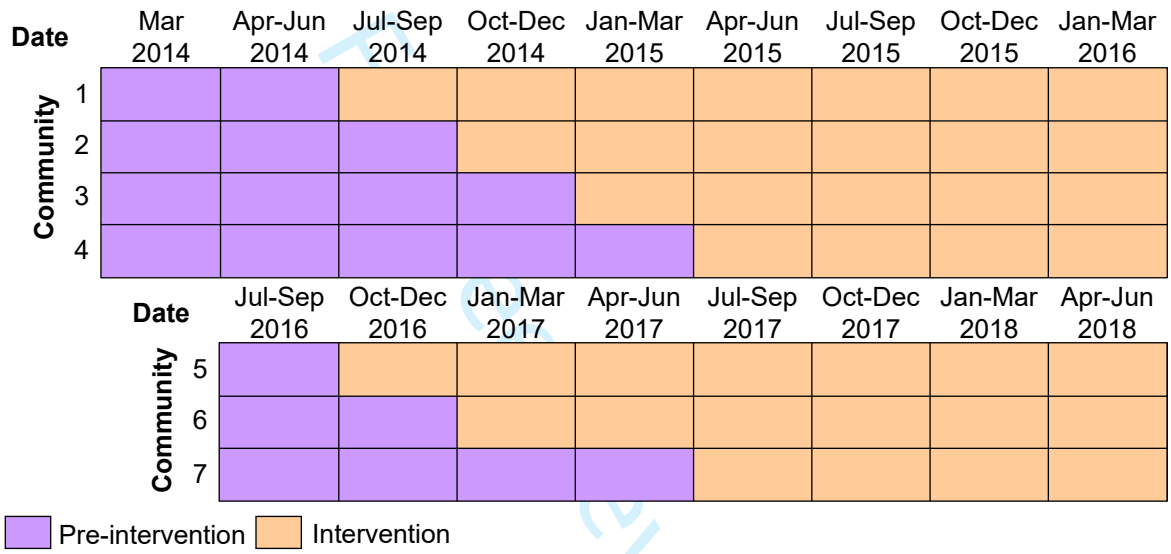


Figure 2 **Flow of participants through the study**

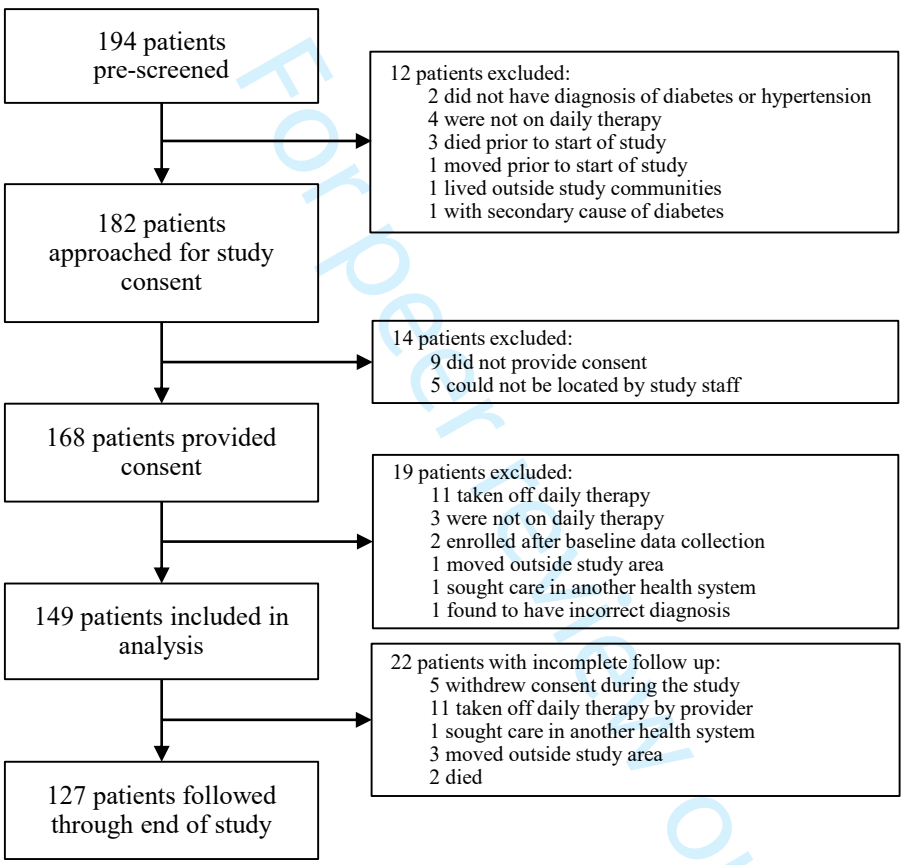
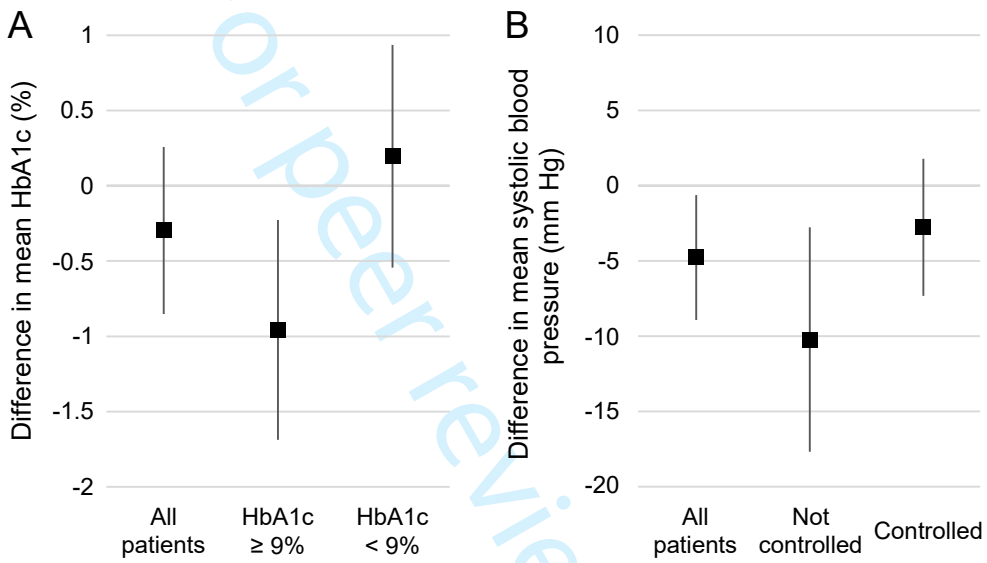


Figure 3 **Diabetes and hypertension continuous outcomes**



Online Supplementary Materials

A community health worker-led intervention decreases glycated haemoglobin and systolic blood pressure in rural Mexico

Supplementary Table 1 Sensitivity Analysis of 2010/2014 vs 2017 Hypertension Guidelines

	2010/2014 Guidelines			2017 Guidelines		
Continuous Outcomes	**n**	**Adjusted OR (95% CI)**	**p-value**	**n**	**Adjusted OR (95% CI)**	**p-value**
Systolic Blood Pressure	117 [869]	-4.7 (-8.9 to -0.6)	0.03	117 [869]	-4.7 (-8.9 to -0.6)	0.03
Not Controlled at baseline	48 [364]	-12.4 (-22.9 to -2.0)	0.02	43 [332]	-9.3 (-17.1 to -1.5)	0.02
Controlled at baseline	62 [486]	-3.5 (-7.6 to 0.6)	0.09	67 [518]	-3.9 (-8.4 to 0.6)	0.09
Diastolic Blood Pressure	117 [869]	-2.2 (-4.5 to 0.1)	0.06	117 [869]	-2.2 (-4.5 to 0.1)	0.06
Not controlled at baseline	48 [364]	-4.6 (-8.5 to -0.7)	0.02	43 [332]	-4.5 (-8.6 to -0.4)	0.03
Controlled at baseline	62 [486]	-1.2 (-3.9 to 1.5)	0.39	67 [518]	-1.6 (-4.3 to 1.1)	0.24
Binary Outcomes	**n**	**Adjusted OR (95% CI)**	**p-value**	**n**	**Adjusted OR (95% CI)**	**p-value**
All Patients	149 [1146]	2.50 (1.26 to 4.99)	0.009	149 [1146]	2.07 (1.03 to 4.14)	0.03
Not controlled at baseline	87 [664]	4.25 (1.42 to 12.70)	0.01	82 [632]	2.75 (1.01 to 7.53)	0.05
Controlled at baseline	61 [477]	2.32 (0.84 to 6.39)	0.1	66 [508]	2.64 (0.88 to 7.95)	0.08
Hypertension	117 [869]	3.18 (1.55 to 6.55)	0.002	117 [869]	2.51 (1.19 to 5.31)	0.02
Not controlled at baseline	48 [364]	6.28 (1.79 to 22.06)	0.004	43 [332]	4.26 (1.31 to 13.89)	0.02
Controlled at baseline	62 [486]	2.65 (0.99 to 7.12)	0.05	67 [518]	3.66 (1.12 to 11.98)	0.03

Primary and secondary hypertension outcomes comparing 2010/2014 with 2017 Mexican Ministry of Health hypertension guidelines (n=number of individual patients [number of time points]). Analysis performed using individual-level mixed effects adjusting for time and cohort with clustering by individual and community. Continuous outcomes presented as adjusted difference in mean between exposed and unexposed with 95% confidence intervals (95% CI) and p-value. Binary outcomes presented as adjusted odds ratio (odds of control in exposed/odds of control in unexposed) with 95% CI and p-value. 2010/2014 guidelines define blood pressure control (in mm Hg) as <140/90, <130/80 if concomitant diabetes, and <150/90 if age ≥ 80.[1] 2017 guidelines define blood pressure control as <140/90 if age <60, <140/80 if concomitant diabetes, and <150/90 if age ≥ 60 (<140/90 if concomitant diabetes).[2]

Supplementary Table 2 Sensitivity analysis modeling community as a fixed effect

Continuous Outcomes	Adjusted estimate (95% CI)	p-value
Diabetes, HbA1c (n=73 [543])	-0.3% (-0.8 to 0.3%)	0.36
Baseline A1c ≥ 9% (n=37 [278])	-1.0% (-1.7 to -0.2%)	0.01
Baseline A1c < 9% (n=36 [265])	0.3% (-0.5 to 1.0%)	0.45
Hypertension, Systolic Blood Pressure (n=117 [869])	-4.2 mmHg (-8.4 to 0 mmHg)	0.05
Not Controlled at Baseline (n=48 [364])	-8.9 mmHg (-16.4 to -1.3 mmHg)	0.02
Controlled at Baseline[a] (n=62 [486])	-1.9 mmHg (-6.5 to 2.7 mmHg)	0.42
Hypertension, Diastolic Blood Pressure (n=117 [869])	-1.9 mmHg (-4.2 to 0.4 mmHg)	0.11
Not Controlled at Baseline (n=48 [364])	-3.8 mmHg (-7.8 to 0.2 mmHg)	0.06
Controlled at Baseline[a] (n=62 [486])	-0.8 mmHg (-3.6 to 1.9 mmHg)	0.56
Binary Outcomes	**Adjusted OR (95% CI)**	**p-value**
All Patients (n=149 [1146])	2.54 (1.25 - 5.14)	0.01
Not Controlled at Baseline (n=87 [664])	4.05 (1.29 - 12.68)	0.02
Controlled at Baseline[b] (n=61 [476])	2.23 (0.78 - 6.37)	0.13
Diabetes (n=73 [543])	2.08 (0.53 - 8.19)	0.30
Not Controlled at Baseline (n=54 [417])	3.97 (0.61 - 25.75)	0.15
Controlled at Baseline[c] (n=15 [108])	1.59 (0.06 - 42.08)	0.78
Hypertension (n=117 [869])	3.00 (1.43 - 6.32)	0.004
Not Controlled at Baseline (n=48 [364])	4.81 (1.30 - 17.73)	0.02
Controlled at Baseline[a] (n=62 [486])	2.25 (0.80 -6.38)	0.13

Primary and secondary outcomes with community modeled as a fixed effect (n=number of individual patients [number of time points]). Analysis performed using individual-level mixed effects adjusting for time, cohort, and community with clustering by individual and community. Continuous outcomes presented as adjusted difference in mean between exposed and unexposed with 95% confidence intervals (95% CI) and p-value. Binary outcomes presented as adjusted odds ratio (odds of control in exposed/odds of control in unexposed) with 95% CI and p-value. [a] Defined as blood pressure (in mm Hg) < 140/90, <130/80 if concomitant diabetes, <150/90 if age ≥ 80 according to Mexican Ministry of Health guidelines.[1] [b] Defined as control of diabetes if diagnosed with diabetes, hypertension if diagnosed with hypertension, or both if dual diagnosis. [c] Defined as glycated haemoglobin (HbA1c) < 7%.

Supplementary Table 3 Sensitivity analysis excluding patients removed from treatment during study period

Continuous Outcomes	Adjusted estimate (95% CI)	p-value
Diabetes, HbA1c (n=72 [537])	-0.2% (-0.8 to 0.4%)	0.48
Baseline A1c ≥ 9% (n=36 [272])	-0.9% (-1.6 to -0.1%)	0.02
Baseline A1c < 9% (n=36 [265])	0.2% (-0.5 to 0.9%)	0.60
Hypertension, Systolic Blood Pressure (n=106 [815])	-4.6 mmHg (-9.0 to -0.1 mmHg)	0.04
Not Controlled at Baseline (n=47 [361])	-9.8 mmHg (-17.3 to -2.3 mmHg)	0.01
Controlled at Baseline[a] (n=53 [436])	-3.7 mmHg (-8.6 to 1.2 mmHg)	0.14
Hypertension, Diastolic Blood Pressure (n=106 [815])	-2.5 mmHg (-5.0 to -0.1 mmHg)	0.04
Not Controlled at Baseline (n=47 [361])	-3.7 mmHg (-7.7 to 0.3 mmHg)	0.07
Controlled at Baseline[a] (n=53 [436])	-2.0 mmHg (-4.9 to 0.9 mmHg)	0.18
Binary Outcomes	**Adjusted OR (95% CI)**	**p-value**
All Patients (n=138 [1088])	2.73 (1.33 - 5.60)	0.006
Not Controlled at Baseline (n=85 [656])	4.07 (1.35 -12.26)	0.01
Controlled at Baseline[b] (n=52 [426])	2.64 (0.92 - 7.59)	0.07
Diabetes (n=72 [537])	2.50 (0.65 - 9.55)	0.18
Not Controlled at Baseline (n=53 [411])	4.81 (0.78 - 29.48)	0.09
Controlled at Baseline[c] (n=15 [108])	1.46 (0.06 - 37.26)	0.82
Hypertension (n=106 [815])	3.41 (1.61 - 7.20)	0.001
Not Controlled at Baseline (n=47 [361])	5.88 (1.67 - 20.71)	0.006
Controlled at Baseline[a] (n=53 [436])	2.98 (1.07 - 8.35)	0.04

Primary and secondary outcomes with exclusion of 11 patients who were removed from treatment by their provider (n=number of individual patients [number of time points]). Analysis performed using individual-level mixed effects adjusting for time and cohort with clustering by individual and community. Continuous outcomes presented as adjusted difference in mean between exposed and unexposed with 95% confidence intervals (95% CI) and p-value. Binary outcomes presented as adjusted odds ratio (odds of control in exposed/odds of control in unexposed) with 95% CI and p-value. [a] Defined as blood pressure (in mm Hg) < 140/90, <130/80 if concomitant diabetes, <150/90 if age ≥ 80 according to Mexican Ministry of Health guidelines.[1] [b] Defined as control of diabetes if diagnosed with diabetes, hypertension if diagnosed with hypertension, or both if dual diagnosis. [c] Defined as glycated haemoglobin (HbA1c) < 7%.

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2. Secretaría de Salud, Mexico. PROYECTO de Norma Oficial Mexicana PROY-NOM-030-SSA2-2017, Para la prevención, detección, diagnóstico, tratamiento y control de la hipertensión arterial sistémica. April, 2017. http://www.dof.gob.mx/nota_detalle.php?codigo=5480159&fecha=19/04/2017 (Accessed 11 Mar 2019).

STROBE Statement

Checklist of items that should be included in reports of observational studies

Section/Topic	Item No	Recommendation	Reported on Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4,5
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4,5
Bias	9	Describe any efforts to address potential sources of bias	5,8
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	5
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	5
		(*e*) Describe any sensitivity analyses	5

Section/Topic	Item No	Recommendation	Reported on Page No
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	Figure 2
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5,6
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	5
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	6,7
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6,7
		(*b*) Report category boundaries when continuous variables were categorized	6,7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7
Discussion			
Key results	18	Summarise key results with reference to study objectives	7,8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8
Generalisability	21	Discuss the generalisability (external validity) of the study results	8
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9

**Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.*

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Observational stepped-wedge analysis of a community health worker-led intervention for diabetes and hypertension in rural Mexico

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Primary Subject Heading:	Global health
Secondary Subject Heading:	Cardiovascular medicine, Diabetes and endocrinology, Public health
Keywords:	Hypertension < CARDIOLOGY, PUBLIC HEALTH, General diabetes < DIABETES & ENDOCRINOLOGY, PRIMARY CARE

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Observational stepped-wedge analysis of a community health worker-led intervention for diabetes and hypertension in rural Mexico

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ABSTRACT

Objectives: There is emerging interest and data supporting the effectiveness of community health workers (CHWs) in noncommunicable diseases (NCDs) in low- and middle-income countries (LMICs). This study aimed to determine whether a CHW-led intervention targeting diabetes and hypertension could improve markers of clinical disease control in rural Mexico.

Design and setting: A prospective observational stepped-wedge study was conducted across seven communities in rural Chiapas, Mexico from March 2014 to April 2018.

Participants: 149 adults with hypertension and/or diabetes.

Intervention: This study was conducted in the context of the programmatic roll-out of an accompaniment-based CHW-led intervention designed to complement comprehensive primary care for adults with diabetes and/or hypertension. Implementation occurred sequentially at three-month intervals with point-of-care data collected at baseline and every three months thereafter for 12 months following roll-out in all communities.

Outcome measures: Primary outcomes were glycated haemoglobin (HbA1c) and systolic blood pressure (SBP), overall and stratified by baseline disease control. We conducted an individual-level analysis using mixed effects regression, adjusting for time, cohort, and clustering at the individual and community levels.

Results: Among patients with diabetes, the CHW-led intervention was associated with a decrease in HbA1c of 0.35%; however, confidence intervals were wide (95%CI -0.90 to 0.20%). In patients with hypertension, there was a 4.7 mmHg decrease in SBP (95%CI -8.9 to -0.6 mmHg). In diabetic patients with HbA1c ≥ 9%, HbA1c decreased by 0.96% (95%CI -1.68 to -0.23%), and in patients with uncontrolled hypertension, SBP decreased by 10.2 mmHg (95%CI -17.7 to -2.8 mmHg).

Conclusions: We found that a CHW-led intervention resulted in clinically meaningful improvement in disease markers for patients with diabetes and hypertension, most apparent among patients with hypertension and patients with uncontrolled disease at baseline. These findings suggest that CHWs can play a valuable role in supporting NCD management in LMICs.

Trial registration: NCT02549495

STRENGTHS AND LIMITATIONS

- This study evaluates a CHW-led intervention, versus comprehensive primary care alone, on measures of clinical disease control among patients with NCDs in Latin America.
- We expand on a prior analysis to quantify the effect of the CHW intervention on clinical indicators of diabetes and hypertension control in an expanded cohort of communities and patients, examining whether the intervention performed differently in patients with poor disease control.
- Utilizing the programmatic stepped roll-out of the CHW intervention allowed for individual-level analysis as in a stepped-wedge trial, limiting confounding by stable individual-level characteristics.
- The stepped wedge design is a practical approach for implementation and evaluation of low-risk interventions expected to confer a large benefit in impoverished settings, limiting the ethical issue of nontreatment common to randomised trials.
- Limitations of this study include small sample size, which may have impacted the precision of several analyses, and evaluation in a single rural, remote region. However, the successes of the intervention in spite of numerous barriers and mounting comparable evidence from LMICs suggest that the findings may be generalisable to other remote, rural settings

INTRODUCTION

71% (42 million) of all deaths worldwide are attributable to noncommunicable diseases (NCDs) including cardiovascular disease and diabetes. Over three-quarters (32 million) of these occur in low- and middle-income countries (LMICs).[1] Poor patients suffer a higher burden of NCD risk factors and worse outcomes, with over 85% of premature deaths from NCDs occurring in LMICs.[1,2]

Community Health Workers (CHWs) have the potential to play a significant role in strengthening health systems worldwide, with increasing interest in their support for NCD management and emerging evidence of their effectiveness.[3,4] Understanding the effect of CHW interventions on biologic markers of disease control is important to help anticipate the effects of successful programs on individual and population health. A 1% reduction in glycated haemoglobin (HbA1c) among patients with diabetes or a 10 mm Hg reduction in systolic blood pressure (SBP) in patients with hypertension has been associated with a reduction in disease-related deaths as well as micro- and macrovascular complications.[5,6]

Until recently, evidence for the ability of CHWs to improve NCD control in LMICs was limited. A recent systematic review of CHWs in LMICs for prevention and management of diabetes found positive outcomes in a majority of studies, but identified significant heterogeneity among structures of CHW interventions and limitations due to study design, high rates of attrition, absence of detailed reporting on operational design, and variable program fidelity.[7] Observational studies of CHW-led interventions demonstrated improvement in fasting plasma glucose,[8,9] though a recent cluster-randomised trial found inconclusive results, potentially due to a lack of power.[10] For cardiovascular disease, two systematic reviews, including one meta-analysis of randomised trials, identified improvements in blood pressure with CHW interventions.[4,11] Several recent cluster-randomised trials around the world demonstrated blood pressure reduction and improved cardiovascular risk control among patients with uncontrolled hypertension.[12-15] Variability in findings across studies could result from heterogeneity in CHW interventions, including CHW roles, which may include disease screening, individual or group disease education, lifestyle management, medication and clinic adherence support, and medication management – with or without assistance of clinic physicians.

In Mexico, ischaemic heart disease and diabetes are the two leading causes of mortality.[16,17] A 2016 national survey estimated that 9.4% and 26% of Mexican adults had diabetes and hypertension, respectively,[18] with low rates of clinical control and increasing prevalence across most demographics.[17-19] The Mexican Ministry of Health (MOH) identifies NCDs and corresponding risk factors as a priority and recognizes the need for scalable, evidence-based interventions that address promotion of healthy behaviours and disease management.[19] While there is no national-level CHW programme in Mexico, national strategies emphasise active community participation in addressing the rising burden of NCDs, advocate for the creation of community committees, and encourage partnership with non-governmental organisations.[17,19] Experience using Mexican *Promotores de Salud* as CHWs focused on education and lifestyle modification has been varied but promising,[20] though they have not yet been widely mobilised to provide individual or instrumental support in NCD management. Compañeros en Salud (CES) is an affiliate of the multinational non-governmental organization Partners in Health. CES works in collaboration with the Mexican Ministry of Health in Chiapas, Mexico, a state with the highest rates of poverty and extreme poverty and one of the lowest rates of effective health coverage in the country.[21] We previously found that a CHW intervention led to improved medication adherence and disease control among patients with diabetes and hypertension.[22] Here we expand on this prior analysis to quantify the effect of the intervention on clinical indicators of diabetes and hypertension control in an expanded cohort of communities and patients, and examined whether the intervention performed differently in patients with poor disease control. We hypothesized that the intervention would reduce HbA1c in patients with diabetes and systolic blood pressure in patients with hypertension.

METHODS

Study Design

This study was structured around the planned programmatic roll-out of a CHW intervention targeting diabetes and hypertension in seven rural, remote communities (population 1000 - 2500) in Chiapas, Mexico where CES operates.

To ensure sufficient time for implementation, including training and supervision of CHWs, the intervention was sequentially implemented at three-month intervals. The first cohort included four communities in which CES had been working for two years. Study enrollment took place during March 2014 with intervention implementation at three month intervals and data collection through January 2016 (figure 1), and we found improved disease control and medication adherence among all patients.[22] However, due to the small sample, the analysis combined patients with diabetes and hypertension and we were unable to quantify the disease-specific clinical effects of the intervention. Based on these findings, the intervention was subsequently scaled to three additional communities in which CES had been supporting primary care for two years. Enrollment took place during July 2016, with implementation and data collection in this cohort through April 2018. In both cohorts, data collection took place at baseline (i.e. prior to implementation in any community) and every three months thereafter for 12 months following implementation of the intervention in all seven communities (figure 1).

This study was reviewed and approved by institutional review boards of the Brigham and Women's Hospital (Partners Human Research Committee) and the Instituto Tecnológico de Monterrey. Participants provided verbal informed consent, which was documented in writing by study staff.

Intervention

CES has partnered with the Mexican Ministry of Health since February 2012 to provide comprehensive primary care and management for patients with NCDs, in accordance with national guidelines. The care model includes monthly clinic visits, disease counseling, and treatment with common oral medications for diabetes and hypertension, which are provided free-of-charge to patients.

The CHW-led intervention follows a community-based accompaniment approach centered on regular home visits. This approach has demonstrated effectiveness in improving disease outcomes and medication adherence in patients with HIV.[23,24] CHWs serve as a bridge between patient and clinic, promoting medication adherence, reinforcing basic disease education, providing psychosocial support, and supporting active case retention. The CHWs in this intervention are women who were nominated at community meetings (by self or community) and selected based on a formal interview process focusing on leadership potential, motivation, basic literacy, and education. They were trained in four-times-weekly group sessions for one month, covering basic pathophysiology, diagnosis, and treatment of chronic diseases including diabetes and hypertension, as well as practical training on the elements of a home visit and the logistical requirements of the role. They also participated in monthly refresher training sessions, covering themes such as motivational interviewing, recognition of emergencies and complications, and navigation of interactions with challenging patients. CHWs work longitudinally with patients, conducting home visits which begin weekly then change in frequency based on a collaborative assessment of the patient's needs by the CHW and clinic physician with a minimum of one visit monthly. Home visits consist of disease counseling with motivational interviewing, assessment of medication adherence and supply, and disease monitoring including blood pressure and capillary glucose measurement. CHWs accompany patients to clinic visits and meet regularly with clinic physicians to discuss patient management. They are compensated with household food and consumable items, worth a dollar amount approximately equivalent to a national conditional cash-transfer programme in place at the time of the program's creation. The overall structure of the CHW-led intervention was the same in both cohorts.

Study Participants

Patients with diabetes, hypertension, and respective risk factors were identified via a CES program of clinic-based and door-to-door case finding. Each community has one health centre staffed by a social service general physician who maintains registries of patients with NCDs, which served as the basis for eligibility determination and recruitment. Eligible patients were those who had a diagnosis of diabetes and/or hypertension, were aged 18 years or older at the time of enrolment, resided in a study community, and were prescribed daily medications by the clinic physician for treatment of diabetes and/or hypertension. We excluded patients with secondary hypertension, type 1 diabetes, pregnancy, and chronic use of glucocorticoids. We also excluded patients who, after enrolment but prior to implementation of the intervention in the first community, were removed from treatment by their physician, moved

outside the study community, transferred care to another health facility, or who were determined not to have a diagnosis of diabetes or hypertension.

Patient and Public Involvement

Patients and the public were not involved in the design, conduct, or reporting of this study.

Data Collection

Study staff visited patient homes and collected data at baseline and three-month intervals thereafter, timed just prior to roll-out of the intervention in a new community. At enrollment, we administered a basic demographic and socioeconomic questionnaire to all patients. Outcomes data measured included systolic and diastolic blood pressure (in mm Hg) among patients with hypertension and HbA1c (in % HbA1c) among patients with diabetes. We measured blood pressure in a seated position using two measurements (bilateral arms) with the Omron HEM 7080IT E automated blood pressure cuff, taking a third measurement if the difference in SBP was ≥ 6 mm Hg. Average systolic blood and diastolic blood pressures were calculated as the mean between the two closest readings. We measured HbA1c using the Bayer A1c NOW point-of-care device. Adverse effects and clinical events (death, myocardial infarction, stroke) were recorded at three-month intervals.

Outcomes

The primary outcomes for this study were HbA1c and systolic blood pressure, analysed as continuous variables. These were analysed among all patients with diabetes and hypertension, respectively, and in subgroups characterized by level of disease control at baseline to assess for effect modification by baseline level of control. We hypothesized that the intervention may offer greater clinical benefit in patients without consistent disease control. For example, while improvement in markers of disease control would be considered a successful outcome among patients with uncontrolled disease, maintenance of disease control, but not necessarily improvement, would be considered a successful outcome among patients with controlled disease. Though not pre-specified by protocol, this stratified analysis was agreed upon by investigators based on clinical applicability prior to initiation of data analysis. Poor diabetes control at baseline was defined as HbA1c ≥ 9%, reflecting the standard of various quality metrics.[25] Disease control among patients with hypertension was defined according to Mexican national guidelines: blood pressure <140/90 mm Hg for patients with hypertension and no diabetes; blood pressure <130/80 mm Hg for patients with hypertension and diabetes and blood pressure <150/90 mm Hg for patients over the age of 80.[17] Secondary outcomes included diastolic blood pressure (DBP), analysed as a continuous variable, and disease control examined as a binary variable (i.e. HbA1c < 7% for diabetic patients per national guidelines and the above thresholds for hypertensive patients). The latter analyses were conducted overall (with disease control defined as control of both diabetes and hypertension if the patient had both diagnoses) and separately by disease.

Statistical methods and data analysis

The study size was limited by the number of patients meeting eligibility criteria in the communities where the intervention was to be implemented. We therefore calculated detectable alternatives with at least 80% power using a sample size calculator that allowed for clustering at the individual and community levels.[26] We assumed an intraperson correlation of 0.7 and intracommunity correlation of 0.05. For expected enrollment of 70 patients with diabetes, we would have >80% power to detect a difference in HbA1c of +/- 0.3%, assuming a baseline HbA1c of 9.5 (SD 2.5). Assuming 110 patients with hypertension, we would have >80% power to detect a difference in systolic blood pressure of +/- 2 mm Hg, assuming a baseline SBP of 140 mm Hg (SD 20). Calculations assumed an alpha of 0.05.

Outcomes assessments for individuals who withdrew from the study for any reason were included until the time at which they withdrew. We conducted individual-level mixed effects analyses including random intercepts for each individual and community to adjust variances for individual repeated measures and clustering by community, respectively.[27-29] The random intercept for community was excluded from the model if the variance for the intercept was zero to avoid overfitting. We modeled continuous outcomes (HbA1c, SBP, DBP) using linear mixed

models with maximum likelihood estimation.[27,29] Binary outcomes were modeled using generalised linear mixed models with Laplace maximum likelihood estimation and a logit link.[28,30] Fixed effects included a binary variable to indicate whether the person lived in a community that was exposed to the intervention at a given time point, a categorical variable for time (i.e. corresponding to each intervention / data collection step) to adjust for secular trends and an indicator variable for cohort (first versus second). We conducted stratified analyses to examine whether any effect of the intervention depended on baseline disease control and calculated p-values for differences in continuous outcomes and odds ratios (ORs) using Cochran's Q-test for heterogeneity. We calculated the intraperson (intracluster) correlation (ICC) of continuous outcomes for patients with two HbA1c or blood pressure measurements collected when unexposed to the intervention.

We performed multiple sensitivity analyses. To examine whether regression to mean could explain the findings of stratified analyses, we repeated stratified analyses removing the baseline value. Because regression to the mean is caused by random error, the measurement following the baseline measurement (i.e. that used to define disease control) would be expected to be closer to the population mean. Thus, if findings of stratified analyses remain similar after excluding the baseline measurement, regression to the mean would be less of a concern. We additionally assessed primary and secondary outcomes using 2017 Mexican MOH guidelines for hypertension featuring more liberal blood pressure targets: <140/80 in patients with hypertension and diabetes, <150/90 if over the age of 60 with hypertension and without diabetes, and <140/90 if over the age of 60 with hypertension and diabetes.[31] To assess for varying trends across communities, we adjusted for community as a fixed effect. We also conducted an analysis in which we modelled time as a random effect with slopes for each cluster (community, individual).[29] Finally, we excluded 11 patients who were removed from treatment by their providers during the study.

Analyses were conducted using SAS V9.4 (Cary Institute, Cary, North Carolina). This study is registered at ClinicalTrials.gov (NCT02549495).

RESULTS

Description of the study cohort and data completeness

We screened 192 patients identified through clinic NCD registries and enrolled 168 patients who provided informed consent in March 2014 (cohort 1) and July 2016 (cohort 2; figure 2). 19 patients (11%) were excluded prior to intervention or analysis. Of the 149 patients analyzed, 39 (26%) had diabetes, 79 (53%) had hypertension, and 31 (21%) had both diseases. The average cluster size was 21 (SD 10). 127 patients (85%) contributed data through the completion of the study. Twenty-two patients withdrew from the study; in eleven, this was due to physician discontinuation of therapy. Of a total 1204 possible data collection time points corresponding to active study participation (i.e. excluding data collection that would have occurred following a withdrawal), we collected data at 1154 time points (96%). Of these, individuals at 397 time points were unexposed to the intervention and 757 were exposed.

Baseline demographic and disease data are presented in table 1. 64% of patients (n=96) were female with a median age of 58 years [IQR 50, 71]. The median HbA1c in patients with diabetes was 9.3 [IQR 7.2, 11.7] with 53% (n=37) having a HbA1c ≥ 9%. 22% of patients (n=15/69) with diabetes had disease control at baseline. The median systolic blood pressure in patients with hypertension was 135 [IQR 126, 151]. 59% of patients (n=61) with hypertension had disease control at baseline. For patients with two time points unexposed to the intervention, the intraperson (intracluster) correlation was 0.77 for systolic blood pressure and 0.78 for diastolic blood pressure (n=86) among patients with hypertension and 0.97 for HbA1c among patients with diabetes (n=55).

Table 1 Baseline characteristics of study participants (n=149) [a]

Community	Overall (n=149)	1 (n=43)	2 (n=24)	3 (n=25)	4 (n=16)	5 (n=16)	6 (n=11)	7 (n=14)
Male, n (%)	53 (36)	19 (44)	5 (21)	6 (24)	7 (44)	6 (38)	3 (27)	7 (50)
Median Age, years [IQR] (n=142)	58 [50, 71]	59 [54, 72]	54 [48, 70]	61 [54, 73]	55 [50, 71]	58 [52, 66]	61 [47, 69]	57 [46, 71]
Has a radio, n (%)	93 (62)	30 (70)	12 (50)	17 (68)	7 (44)	13 (81)	5 (45)	9 (64)
Has a car/ motorcycle, n (%)	43 (29)	8 (19)	6 (25)	11 (44)	4 (25)	3 (19)	5 (45)	6 (43)
Type of remuneration								
Salary, n (%)	8 (5)	1 (2)	0 (0)	1 (4)	4 (25)	0 (0)	0 (0)	2 (14)
Day Labour, n (%)	58 (39)	15 (35)	9 (38)	5 (20)	2 (13)	11 (69)	9 (82)	7 (50)
None, n (%)	83 (56)	27 (63)	15 (63)	19 (76)	10 (63)	5 (31)	2 (18)	5 (36)
Diabetes Diagnosis, n (%)	70 (47)	28 (65)	12 (50)	6 (24)	9 (56)	10 (63)	2 (18)	3 (21)
HbA1c (%), median [IQR]	9.3 [7.2, 11.7]	8.1 [7.1, 10.6]	11.7 [9.3, 13]	7.9 [7.8, 9.3]	11.3 [10.0, 13.0]	8.8 [7.0, 12.6]	8.1 [6.3, 9.9]	6.2 [5.1, 10.3]
HbA1c ≥ 9%, n (%)	37 (53)	11 (39)	9 (75)	2 (33)	8 (89)	5 (50)	1 (50)	1 (33)
Controlled Diabetes[b], n (%) (n=69)	15 (22)	7 (26)	1 (8)	1 (17)	0 (0)	3 (30)	1 (50)	2 (67)
Hypertension Diagnosis, n (%)	110 (74)	34 (79)	12 (50)	23 (92)	7 (44)	13 (81)	10 (91)	12 (86)
Systolic BP (mm Hg), median [IQR]	135 [126, 151]	130 [117, 146]	150 [125, 173]	135 [120, 145]	145 [132, 197]	146 [138, 151]	139 [144, 151]	132 [126, 138]
Diastolic BP (mm Hg), median [IQR]	80 [72, 88]	77 [69, 86]	84 [74, 93]	79 [72, 85]	89 [71, 105]	82 [79, 92]	86 [84, 91]	77 [73, 82]
Controlled Hypertension[c], n (%)	61 (59)	20 (59)	5 (42)	16 (73)	2 (29)	5 (38)	5 (50)	9 (75)

[a] Unless otherwise stated. [b] Defined as glycated haemoglobin (HbA1c) < 7%. [c] Defined as blood pressure (in mm Hg) < 140/90, <130/80 if concomitant diabetes, <150/90 if age ≥ 80 according to 2010/2014 Mexican Ministry of Health guidelines.[17]

Continuous Outcomes of HbA1c and Blood Pressure

In adjusted analysis, among 73 patients with diabetes, there was a decrease in HbA1c of 0.35% with exposure to the intervention (figure 3a); however, confidence intervals were wide (95% CI -0.90 to 0.20%, p=0.21). Among 117 patients with hypertension, there was a 4.7 mm Hg decrease in systolic blood pressure with exposure to the intervention (95% CI -8.9 to -0.6 mm Hg, p=0.03, figure 3b) and a 2.2 mm Hg decrease in diastolic blood pressure (95% CI -4.5 to 0.1 mm Hg, p=0.056).

In patients with diabetes with HbA1c ≥ 9% at baseline (n=37), relative to no intervention, exposure to the CHW intervention resulted in a decrease in HbA1c of 0.96% (95% CI -1.68 to -0.23%, p=0.01, figure 3a). There was no evidence of a clinically significant intervention effect among patients with HbA1c < 9% at baseline (estimate 0.11%, 95% CI -0.62 to 0.84%, p=0.76, n=32; p-value for interaction: 0.04).

In patients with uncontrolled hypertension at baseline (n=48), exposure to the intervention resulted in a 10.2 mm Hg decrease in systolic blood pressure (95% CI -17.7 to -2.8 mm Hg, p=0.007, figure 3b) relative to no intervention. Among patients with baseline hypertension control (n=62), the intervention was associated with a reduction of 2.8 mm Hg (95% CI -7.3 to 1.8 mm Hg, p=0.23; p-value for interaction: 0.09). Similar results were observed for diastolic blood pressure: patients with uncontrolled baseline hypertension had a 4.6 mm Hg decrease (95% CI -8.5 to

-0.7 mm Hg, p=0.02) and patients with baseline control 1.2 mm Hg (95% CI -3.9 to 1.5 mm Hg, p=0.39; p-value for interaction: 0.16).

Binary Outcomes of Controlled Diabetes and Hypertension

In patients with diabetes, we observed a 2.7-fold increase in odds of disease control with receipt of the intervention, relative to none; however, confidence intervals were wide and included one (adjusted OR 2.69, 95% CI 0.72 to 10.14, p=0.14, n=73, table 2). Among patients with hypertension, the intervention was associated with a 3.2-fold increase in the odds of disease control (adjusted OR 3.18, 95% CI 1.55 to 6.55, p=0.002, n=117).

Overall, we observed a greater effect of the intervention among patients with uncontrolled disease at baseline; however, small numbers limited power for statistical comparisons. The effect was larger among patients with uncontrolled diabetes at baseline (adjusted OR 5.35, 95% CI 0.89 to 32.17, p=0.07, n=54) as compared to baseline disease control (adjusted OR 1.46, 95% CI 0.06 to 37.26, p=0.82, n=15; p-value for interaction: 0.49). We also observed a greater effect among patients with uncontrolled hypertension at baseline (adjusted OR 6.28, 95% CI 1.79 to 22.06, p=0.004, n=48) than among patients with baseline controlled hypertension (adjusted OR 2.65, 95% CI 0.99 to 7.12, p=0.05, n=62; p-value for interaction: 0.29).

Table 2 Intervention effectiveness, stratified by disease and baseline disease control

	Adjusted OR (95% CI)	p-value	Interaction
Diabetes (n=73 [543])	2.69 (0.72 - 10.14)	0.14	
Not Controlled at Baseline (n=54 [417])	5.35 (0.89 - 32.17)	0.07	0.49
Controlled at Baseline[a] (n=15 [109])	1.46 (0.06 - 37.26)	0.82	
Hypertension (n=117 [869])	3.18 (1.55 - 6.55)	0.002	
Not Controlled at Baseline (n=48 [364])	6.28 (1.79 - 22.06)	0.004	0.29
Controlled at Baseline[b] (n=62 [486])	2.65 (0.99 - 7.12)	0.053	

Individual-level mixed effects analysis adjusting for time and cohort with random intercepts to account for clustering by individual and community (n=number of individual patients [number of time points]). Four patients with diabetes and seven patients with hypertension not included in stratified analysis due to missing baseline control data. [a] Defined as glycated haemoglobin (HbA1c) < 7%. [b] Defined as blood pressure (in mm Hg) < 140/90, < 130/80 if concomitant diabetes, < 150/90 if age ≥ 80 according to 2010/2014 Mexican Ministry of Health guidelines.[17]

Sensitivity analysis

Results from sensitivity analyses (supplementary tables 1-5) were consistent with primary analyses and did not change interpretation of the findings.

Adverse effects

There were no adverse effects attributable to the CHW intervention.

DISCUSSION

Our findings suggest that when a CHW-led intervention, built around the values of accompaniment,[32] is added to comprehensive primary care in rural Mexico, patients with diabetes and hypertension can experience clinically significant improvements in markers of disease control. This includes a reduction in systolic blood pressure among patients with hypertension, especially those with uncontrolled hypertension, and uncontrolled diabetes (HbA1c ≥ 9%). For patients with diabetes, precision was limited, and confidence intervals were wider than for systolic blood pressure. These findings suggest that the intervention was most effective for those in greatest need.

Our results are consistent with the growing literature of from LMICs supporting the role of CHWs in improving cardiovascular disease risk.[11-15]. Our study differs from many existing studies conducted among patients with

newly-diagnosed or uncontrolled disease in that we implemented the intervention in a population that included both controlled and uncontrolled patients already on pharmacologic treatment. The 10 mm Hg reduction in systolic blood pressure we observed among patients with uncontrolled hypertension is on par with recent cluster randomised trials from India (-8.9 mm Hg),[11] Argentina (-6.6 mm Hg),[13] Colombia and Malaysia (-11.5 mm Hg).[15] Our study further adds to the literature by supporting the role for CHWs in patients with diabetes, where studies have produced promising but sometimes inconclusive results.[9-11]

The CHW intervention was implemented on top of a highly functional primary healthcare system. CHW presence likely contributed to more continuous medication adjustments, improved adherence, and potentially lifestyle changes. That this intervention was most effective in those with poor control at baseline suggests that these tasks help such patients better utilize the care available to them, which is relevant to both high-income contexts and LMICs. In contrast, management of patients with baseline control requires maintenance, potentially achieved by CHW support and response to lapses in disease control. Although our results suggest a stronger effect among uncontrolled patients, our experience suggests that CHWs may learn and benefit from interactions with patients who are able to achieve clinical control. Additionally, disease control in NCDs like diabetes and hypertension can be dynamic, fluctuating over time for an individual patient and posing an increased risk of complications.[33] For these reasons, we advocate CHW interventions targeting all patients and, at minimum, the most socially vulnerable, not only those with the worst control. We anticipate that further addressing social determinants, such as the provision of medically-tailored meals,[34] stable housing, income assistance, and mental health supports, will yield even greater results.

The clinical benefits of CHW interventions in patients with uncontrolled diabetes or hypertension are similar to those associated with the addition of medications to treatment regimens.[6,35] The magnitude of intervention effect observed could significantly reduce diabetes- and hypertension-associated morbidity and mortality. By allocating healthcare financing to human-mediated inputs such as paying, training, and supporting CHWs in addition to medication supplies, there are ancillary benefits for society including empowerment of women, economic stimulation, and decreased unemployment. Any approach that aims to comprehensively address the social determinants of disease and improve outcomes will require new investments in order to build and finance truly functional health systems. The emergence of mobile health technologies may allow for further programmatic and health systems coordination, targeting attrition and providing real-time feedback, with further study needed to assess their role as well as ideal models of CHW task load and supervision structure.

We evaluated this intervention in the context of a programmatic stepped roll-out, in which patients initiated the intervention during the follow-up period. This approach allowed us to rule out confounding by stable individual-level characteristics and adjust for underlying time trends. Secular trends and regression to the mean are common concerns in longitudinal analyses; however, adjustment for time would minimize these potential biases. The high correlation of adjacent measurements, together with sensitivity analyses that supported primary findings and effect estimates in the same direction in both strata, suggest that regression to the mean is unlikely to explain the results of stratified analyses. However, the small sample size may have limited statistical comparisons across subgroups. The use of objective markers of disease control, HbA1c and blood pressure, support the robustness of our findings – any influence being observed (i.e. Hawthorne effect) would likely be apparent in both arms, and therefore would not explain our study findings. Our CHW intervention set minimum standards for visit frequency, but was not designed to assess visit length, frequency, or number of tasks per visit and did not map individual CHWs to patients. These program characteristics may impact the success of a CHW intervention and future studies could facilitate optimization. A lack of data that linked CHWs to patients also precluded adjustment for clustering at the CHW level, which would be important if some CHWs were more or less effective. However, standardization of training, practices, and supervision should have limited variability among CHWs. Our intervention was evaluated in a single rural, remote setting, with limited phone and internet access, dirt roads, and long distances to higher levels of care. The success of the intervention despite these barriers and with comparable evidence from LMICs suggest that the findings may be generalisable to other remote, rural settings.

In conclusion, we demonstrate that an integrated CHW-led intervention targeting NCDs in rural Mexico can improve measures of disease in patients with uncontrolled diabetes and hypertension. Programmes and health

systems aiming to improve care of patients with NCDs may consider this study as supportive evidence for the addition of CHWs to strengthen rural primary care systems in LMICs.

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Contributors: DTW oversaw data collection, carried out the analysis, produced figures and tables, led the literature search, and drafted the manuscript. MF, HF, LP, PMN, and DP contributed to study design. JK and KR led data collection teams. DTW, RB, ZG, JM, and PMN oversaw the data collection process and ensured data quality. MF was the lead methodologist, designed the analysis, and critically reviewed the manuscript. JK contributed to the literature search and manuscript preparation. PMN and DP are responsible for the original conceptualisation, study oversight, and critical review of the manuscript as principal investigators. All authors contributed to interpretation of the work, editing of the manuscript, final approval of this version, and agree to be accountable for all aspects of the work.

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FIGURE LEGENDS

Figure 1 Stepped-wedge schematic for the study

Programmatic roll-out was randomised by community (cluster) with sequential implementation of the intervention resulting in each community contributing time as unexposed (purple) and exposed (peach) to the CHW-led intervention. Data were collected at the start of each 3-month time point across two cohorts regardless of whether the intervention had been implemented. In the first cohort (communities 1-4), data collection took place from March 2014 through January 2016. In the second cohort (communities 5-7), data collection took place from July 2016 through April 2018. Delays in baseline data collection in cohort 1 shortened the duration of period 1 from three

months to one month. Organizational delay in roll-out for cohort 2 shortened the baseline pre-randomisation phase and resulted in a 3-month delay in implementation in community 7.

Figure 2 **Flow of participants through the study**

Figure 3 **Diabetes and hypertension continuous outcomes**

Adjusted mean difference between exposed and unexposed for glycated haemoglobin (HbA1c) among patients with diabetes (A) and average systolic blood pressure in patients with hypertension (B). Individual-level mixed effects analysis adjusting for time and cohort with clustering by individual and community presented as estimate (square) and 95% confidence intervals (lines). A. Diabetes outcomes among all patients (n=73 [543 timepoints]) and dichotomized between poorly controlled (HbA1c ≥ 9%, n=37 [278]) and not poorly controlled (HbA1c < 9%, n=32 [247]) at baseline. B. Hypertension outcomes among all patients (n=117 [869 time points] and dichotomized between not controlled (n=49 [364]) and controlled (blood pressure (in mm Hg) < 140/90, < 130/80 if concomitant diabetes, < 150/90 if age ≥ 80 according to 2010/2014 Mexican Ministry of Health guidelines,[16] n=62 [486]) at baseline. Four patients with diabetes and seven patients with hypertension not included in stratified analysis due to missing baseline control data.

Figure 1 **Stepped-wedge schematic for the study**

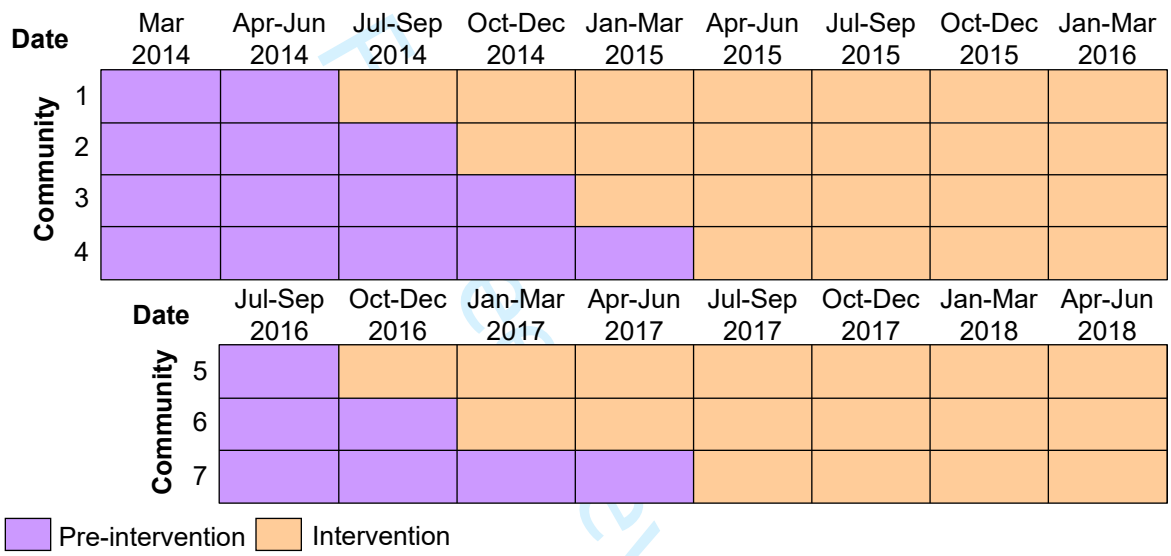


Figure 2 **Flow of participants through the study**

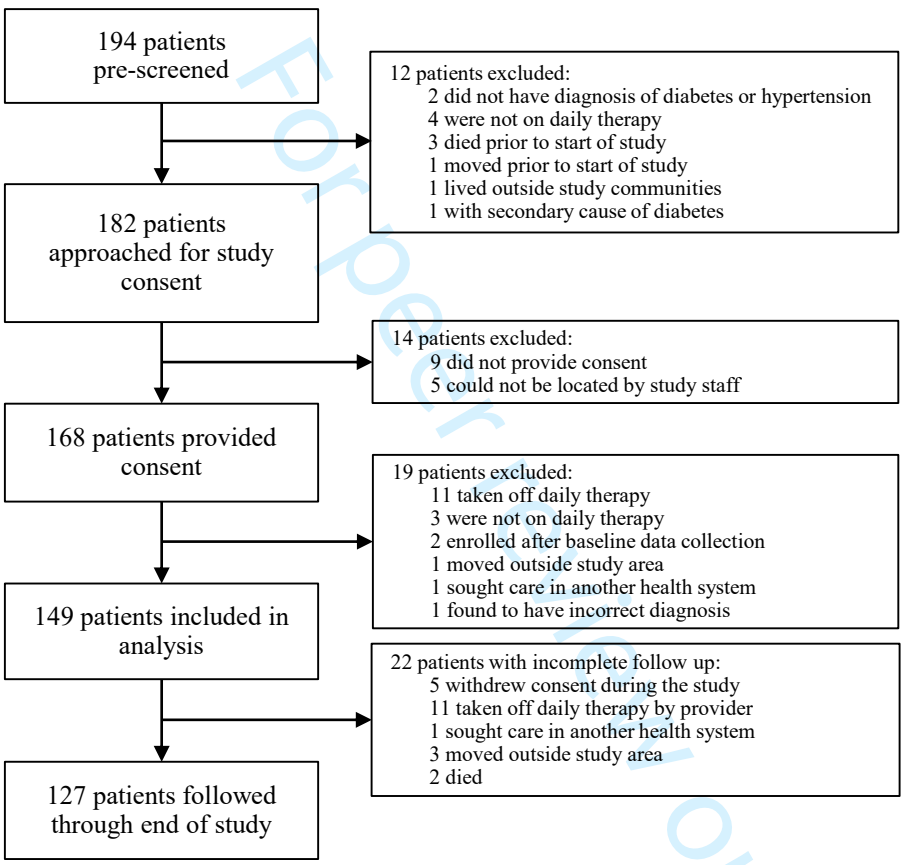
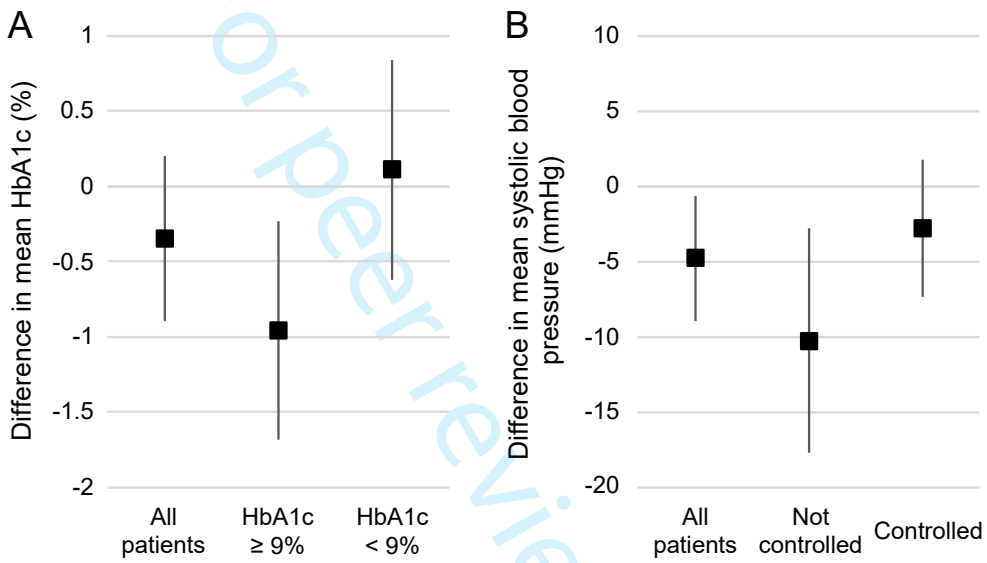


Figure 3 **Diabetes and hypertension continuous outcomes**



Online Supplementary Materials

Observational stepped-wedge analysis of a community health worker-led intervention for diabetes and hypertension in rural Mexico

Supplementary Table 1 Sensitivity analysis with exclusion of baseline measurements

Continuous Outcomes	Adjusted estimate (95% CI)	p-value
Diabetes, HbA1c (n=72 [474])	-0.30% (-0.86 to 0.26%)	0.30
Baseline A1c ≥ 9% (n=36 [241])	-0.88% (-1.63 to -0.12%)	0.02
Baseline A1c < 9% (n=36 [233])	0.26% (-0.51 to 1.04%)	0.50
Hypertension, Systolic Blood Pressure (n=116 [759])	-2.8 mmHg (-7.1 to 1.4 mmHg)	0.19
Not Controlled at Baseline (n=47 [316])	-7.6 mmHg (-15.7 to 0.5 mmHg)	0.07
Controlled at Baseline[a] (n=62 [424])	-2.1 mmHg (-6.9 to 2.7 mmHg)	0.39
Hypertension, Diastolic Blood Pressure (n=116 [759])	-1.5 mmHg (-3.8 to 0.9 mmHg)	0.23
Not Controlled at Baseline (n=47 [316])	-3.4 mmHg (-7.7 to 0.8 mmHg)	0.11
Controlled at Baseline[a] (n=62 [424])	-1.0 mmHg (-3.8 to 1.8 mmHg)	0.49
Binary Outcomes	**Adjusted OR (95% CI)**	**p-value**
Diabetes (n=72 [474])	2.71 (0.68 – 10.93)	0.16
Not Controlled at Baseline (n=53 [363])	4.90 (0.81 - 29.84)	0.08
Controlled at Baseline[b] (n=15 [93])	0.88 (0.02 – 35.41)	0.94
Hypertension (n=116 [759])	2.65 (1.25 - 5.61)	0.01
Not Controlled at Baseline (n=47 [316])	4.83 (1.34 - 17.46)	0.02
Controlled at Baseline[a] (n=62 [424])	2.64 (0.96 – 7.28)	0.06

Primary and secondary outcomes with exclusion of baseline data for patients used to dichotomize based on disease control (n=number of individual patients [number of time points]). Analysis performed using individual-level mixed effects adjusting for time and cohort with clustering by individual and community. Continuous outcomes presented as adjusted difference in mean between exposed and unexposed with 95% confidence intervals (95% CI) and p-value. Binary outcomes presented as adjusted odds ratio (odds of control in exposed/odds of control in unexposed) with 95% CI and p-value. Two patients (one with diabetes, one with hypertension) in primary analysis not included because they contributed data only to the baseline time point. [a] Defined as blood pressure (in mm Hg) < 140/90, < 130/80 if concomitant diabetes, < 150/90 if age ≥ 80 according to Mexican Ministry of Health guidelines.[1] [b] Defined as glycated haemoglobin (HbA1c) < 7%.

Supplementary Table 2 Sensitivity analysis of 2010/2014 vs 2017 hypertension guidelines

	2010/2014 Guidelines			2017 Guidelines		
Continuous Outcomes	**n**	**Adjusted Estimate (mm Hg, 95% CI)**	**p-value**	**n**	**Adjusted Estimate (mm Hg, 95% CI)**	**p-value**
Systolic Blood Pressure	117 [869]	-4.7 (-8.9 to -0.6)	0.03	117 [869]	-4.7 (-8.9 to -0.6)	0.03
Not Controlled at baseline	48 [364]	-12.4 (-22.9 to -2.0)	0.02	43 [332]	-9.3 (-17.1 to -1.5)	0.02
Controlled at baseline	62 [486]	-3.5 (-7.6 to 0.6)	0.09	67 [518]	-3.9 (-8.4 to 0.6)	0.09
Diastolic Blood Pressure	117 [869]	-2.2 (-4.5 to 0.1)	0.06	117 [869]	-2.2 (-4.5 to 0.1)	0.06
Not controlled at baseline	48 [364]	-4.6 (-8.5 to -0.7)	0.02	43 [332]	-4.5 (-8.6 to -0.4)	0.03
Controlled at baseline	62 [486]	-1.2 (-3.9 to 1.5)	0.39	67 [518]	-1.6 (-4.3 to 1.1)	0.24
Binary Outcomes	**n**	**Adjusted OR (95% CI)**	**p-value**	**n**	**Adjusted OR (95% CI)**	**p-value**
Hypertension	117 [869]	3.18 (1.55 to 6.55)	0.002	117 [869]	2.51 (1.19 to 5.31)	0.02
Not controlled at baseline	48 [364]	6.28 (1.79 to 22.06)	0.004	43 [332]	4.26 (1.31 to 13.89)	0.02
Controlled at baseline	62 [486]	2.65 (0.99 to 7.12)	0.053	67 [518]	3.66 (1.12 to 11.98)	0.03

Primary and secondary hypertension outcomes comparing 2010/2014 with 2017 Mexican Ministry of Health hypertension guidelines (n=number of individual patients [number of time points]). Analysis performed using individual-level mixed effects adjusting for time and cohort with clustering by individual and community. Continuous outcomes presented as adjusted difference in mean between exposed and unexposed with 95% confidence intervals (95% CI) and p-value. Binary outcomes presented as adjusted odds ratio (odds of control in exposed/odds of control in unexposed) with 95% CI and p-value. Seven patients with hypertension not included in stratified analysis due to missing baseline control data. 2010/2014 guidelines define blood pressure control (in mm Hg) as < 140/90, < 130/80 if concomitant diabetes, and < 150/90 if age ≥ 80.[1] 2017 guidelines define blood pressure control as < 140/90 if age < 60, < 140/80 if concomitant diabetes, and < 150/90 if age ≥ 60 (<140/90 if concomitant diabetes).[2]

Supplementary Table 3 Sensitivity analysis modeling community as a fixed effect

Continuous Outcomes	Adjusted estimate (95% CI)	p-value
Diabetes, HbA1c (n=73 [543])	-0.26% (-0.82 to 0.30%)	0.36
Baseline A1c ≥ 9% (n=37 [278])	-0.96% (-1.70 to -0.21%)	0.01
Baseline A1c < 9% (n=32 [247])	0.17% (-0.58 to 0.92%)	0.66
Hypertension, Systolic Blood Pressure (n=117 [869])	-4.2 mmHg (-8.4 to -0.03 mmHg)	0.048
Not Controlled at Baseline (n=48 [364])	-8.9 mmHg (-16.4 to -1.3 mmHg)	0.02
Controlled at Baseline[a] (n=62 [486])	-1.9 mmHg (-6.5 to 2.7 mmHg)	0.42
Hypertension, Diastolic Blood Pressure (n=117 [869])	-1.9 mmHg (-4.2 to 0.4 mmHg)	0.11
Not Controlled at Baseline (n=48 [364])	-3.8 mmHg (-7.8 to 0.2 mmHg)	0.06
Controlled at Baseline[a] (n=62 [486])	-0.8 mmHg (-3.6 to 1.9 mmHg)	0.56
Binary Outcomes	**Adjusted OR (95% CI)**	**p-value**
Diabetes (n=73 [543])	2.08 (0.53 to 8.19)	0.30
Not Controlled at Baseline (n=54 [417])	3.97 (0.61 to 25.75)	0.15
Controlled at Baseline[b] (n=15 [108])	1.59 (0.06 to 42.08)	0.78
Hypertension (n=117 [869])	3.00 (1.43 to 6.32)	0.004
Not Controlled at Baseline (n=48 [364])	4.81 (1.30 to 17.73)	0.02
Controlled at Baseline[a] (n=62 [486])	2.25 (0.80 to 6.38)	0.13

Primary and secondary outcomes with community modeled as a fixed effect (n=number of individual patients [number of time points]). Analysis performed using individual-level mixed effects adjusting for time, cohort, and community with clustering by individual and community. Continuous outcomes presented as adjusted difference in mean between exposed and unexposed with 95% confidence intervals (95% CI) and p-value. Binary outcomes presented as adjusted odds ratio (odds of control in exposed/odds of control in unexposed) with 95% CI and p-value. Four patients with diabetes and seven patients with hypertension not included in stratified analysis due to missing baseline control data. [a] Defined as blood pressure (in mm Hg) < 140/90, < 130/80 if concomitant diabetes, < 150/90 if age ≥ 80 according to Mexican Ministry of Health guidelines.[1] [b] Defined as glycated haemoglobin (HbA1c) < 7%.

Supplementary Table 4 Sensitivity analysis adjusted for time as a random effect

Continuous Outcomes	Adjusted estimate (95% CI)	p-value
Diabetes, HbA1c (n=73 [543])	-0.35% (-0.90 to 0.20%)	0.21
Baseline A1c ≥ 9% (n=37 [278])	-0.96% (-1.69 to -0.23%)	0.01
Baseline A1c < 9% (n=32 [247])	0.11% (-0.62 to 0.84%)	0.76
Hypertension, Systolic Blood Pressure (n=117 [869])	-6.0 mmHg (-11.2 to -0.4 mmHg)	0.04
Not Controlled at Baseline (n=48 [364])	-10.3 mmHg (-18.4 to -2.2 mmHg)	0.01
Controlled at Baseline[a] (n=62 [486])	-2.8 mmHg (-7.3 to 1.7 mmHg)	0.23
Hypertension, Diastolic Blood Pressure (n=117 [869])	-2.6 mmHg (-5.4 to 0.1 mmHg)	0.06
Not Controlled at Baseline (n=48 [364])	-4.6 mmHg (-8.8 to -0.5 mmHg)	0.03
Controlled at Baseline[a] (n=62 [486])	-1.2 mmHg (-3.9 to 1.5 mmHg)	0.39

Primary and secondary continuous outcomes with time modeled as a random effect to adjust for random secular trends by cluster (n=number of individual patients [number of time points]). Analysis performed using individual-level mixed effects adjusting for time and cohort with clustering by individual and community with random slopes for time. Continuous outcomes presented as adjusted difference in mean between exposed and unexposed with 95% confidence intervals (95% CI) and p-value. Seven patients with hypertension not included in stratified analysis due to missing baseline control data. [a] Defined as blood pressure (in mm Hg) < 140/90, < 130/80 if concomitant diabetes, < 150/90 if age ≥ 80 according to Mexican Ministry of Health guidelines.[1]

Supplementary Table 5 Sensitivity analysis excluding patients removed from treatment during study period

Continuous Outcomes	Adjusted estimate (95% CI)	p-value
Diabetes, HbA1c (n=72 [537])	-0.29% (-0.84 to 0.26%)	0.30
Baseline A1c ≥ 9% (n=36 [272])	-0.88% (-1.61 to -0.15%)	0.02
Baseline A1c < 9% (n=32 [247])	0.11% (-0.62 to 0.84%)	0.76
Hypertension, Systolic Blood Pressure (n=106 [815])	-5.0 mmHg (-9.4 to -0.6 mmHg)	0.03
Not Controlled at Baseline (n=47 [361])	-9.8 mmHg (-17.3 to -2.3 mmHg)	0.01
Controlled at Baseline[a] (n=53 [436])	-3.7 mmHg (-8.6 to 1.2 mmHg)	0.14
Hypertension, Diastolic Blood Pressure (n=106 [815])	-2.8 mmHg (-5.2 to -0.4 mmHg)	0.02
Not Controlled at Baseline (n=47 [361])	-4.5 mmHg (-8.5 to -0.5 mmHg)	0.03
Controlled at Baseline[a] (n=53 [436])	-2.3 mmHg (-5.1 to 0.6 mmHg)	0.12
Binary Outcomes	**Adjusted OR (95% CI)**	**p-value**
Diabetes (n=72 [537])	2.50 (0.65 - 9.55)	0.18
Not Controlled at Baseline (n=53 [411])	4.81 (0.78 - 29.48)	0.09
Controlled at Baseline[b] (n=15 [108])	1.46 (0.06 - 37.26)	0.82
Hypertension (n=106 [815])	3.41 (1.61 - 7.20)	0.001
Not Controlled at Baseline (n=47 [361])	5.88 (1.67 - 20.71)	0.006
Controlled at Baseline[a] (n=53 [436])	2.98 (1.07 - 8.35)	0.04

Primary and secondary outcomes with exclusion of 11 patients who were removed from treatment by their provider (n=number of individual patients [number of time points]). Analysis performed using individual-level mixed effects adjusting for time and cohort with clustering by individual and community. Continuous outcomes presented as adjusted difference in mean between exposed and unexposed with 95% confidence intervals (95% CI) and p-value. Binary outcomes presented as adjusted odds ratio (odds of control in exposed/odds of control in unexposed) with 95% CI and p-value. Four patients with diabetes and six patients with hypertension not included in stratified analysis due to missing baseline control data. [a] Defined as blood pressure (in mm Hg) < 140/90, < 130/80 if concomitant diabetes, < 150/90 if age ≥ 80 according to Mexican Ministry of Health guidelines.[1] [b] Defined as glycated haemoglobin (HbA1c) < 7%.

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2. Secretaría de Salud, Mexico. PROYECTO de Norma Oficial Mexicana PROY-NOM-030-SSA2-2017, Para la prevención, detección, diagnóstico, tratamiento y control de la hipertensión arterial sistémica. April, 2017. http://www.dof.gob.mx/nota_detalle.php?codigo=5480159&fecha=19/04/2017 (accessed 11 Mar 2019).

STROBE Statement

Checklist of items that should be included in reports of observational studies

Section/Topic	Item No	Recommendation	Reported on Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4,5
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4,5
Bias	9	Describe any efforts to address potential sources of bias	5,8
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	5
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	5
		(*e*) Describe any sensitivity analyses	5

Section/Topic	Item No	Recommendation	Reported on Page No
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	Figure 2
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5,6
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	5
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	6,7
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6,7
		(*b*) Report category boundaries when continuous variables were categorized	6,7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7
Discussion			
Key results	18	Summarise key results with reference to study objectives	7,8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8
Generalisability	21	Discuss the generalisability (external validity) of the study results	8
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9

**Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.*

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.