Effect of a multifaceted mobile technology enabled primary care intervention on cardiovascular disease risk management in rural Indonesia: a quasi-experimental study

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Effect of a multifaceted mobile technology enabled primary care intervention on cardiovascular disease risk management in rural Indonesia: a quasi-experimental study

Short title: *Patel et al.;* A mHealth enabled intervention to prevent CVD

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Key points (75-100 words)

Question: Is a mobile technology-supported primary healthcare intervention associated with greater use of preventive drug treatments compared to usual care among individuals at high cardiovascular disease risk?

Findings: In this quasi-experimental study involving 8 villages and 6579 high-risk people in rural Indonesia, 15.5% of individuals in the intervention villages reported use of appropriate use of preventive medications compared with 1.0% in the control villages. The difference in blood pressure lowering drug use was 57% vs. 16%.

Meaning: The primary healthcare intervention was associated with increased use of preventive drug therapies in people with high predicted cardiovascular disease risk.

(98 words)

Abstract

Importance: Cardiovascular diseases (CVD) are the leading cause of disease burden in Indonesia. Implementation of effective interventions for CVD prevention is limited.

Objective: To evaluate whether a mobile technology-supported primary healthcare intervention would improve use of preventive drug treatment among people with high CVD risk, vs usual care.

Design: Quasi-experimental study involving four intervention and four control villages conducted between September 2016 and March 2018. Median duration of follow-up was 12.2 months.

Setting: Malang district, Indonesia

Participants: Residents aged ≥40 years were invited to participate. Those with high predicted 10-year CVD risk (previous diagnosed CVD; systolic blood pressure (BP) >160 mmHg or diastolic BP >100 mmHg; 10-year predicted CVD risk ≥ 30%; or 10-year predicted CVD risk of 20-29% and a systolic BP>140 mmHg) were followed.

Intervention: A multi-faceted mobile technology-supported intervention facilitating community-based CVD risk screening with referral, tailored clinical decision support for drug prescription and patient follow-up.

Main outcomes and measures: The primary outcome was the proportion on appropriate preventive CVD medications, defined as at least one BP lowering drug and a statin for all high-risk individuals, and an antiplatelet drug for those with prior diagnosed CVD. Secondary outcomes included mean change in BP from baseline.

Results: Among 22,635 adults, 3494 (29.9%) and 3085 (28.1%) had high predicted CVD risk in the intervention and control villages, respectively. Of these, follow-up was completed in 2632 (75.3%) from intervention villages and 2429 (78.7%) from control villages. At follow-up, 15.5% of high-risk individuals in intervention villages were taking appropriate preventive

CVD medications, compared with 1.0% of in control villages (adjusted risk difference, 14.1%, [95% CI, 12.7% to 15.6%]). This difference was driven by higher BP lowering treatment use (56.8% vs. 15.7%; adjusted risk difference, 39.4% [95% CI, 37.0% to 41.7%). The adjusted mean difference in change in systolic BP from baseline was -8.3 mmHg, [95% CI, -6.6 to -10.1 mmHg]).

Conclusions and relevance: A multi-faceted mobile technology supported primary healthcare intervention was associated with greater use of preventive CVD medication use and lower BP levels among high-risk individuals in a rural Indonesian population.

Clinical Trial Registration

Clinical Trial Registry of India,

http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=16655

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Introduction

The high cardiovascular diseases (CVD) burden in low- and middle-income countries has increased the need for health systems to deliver effective preventive care [1-3]. Emphasis has been placed on strengthening primary healthcare systems traditionally orientated towards maternal and child healthcare and acute episodic care for infectious diseases [4, 5]. Mobile health (mHealth) solutions may facilitate this reorientation and primary healthcare system strengthening. However, a 2014 systematic review examining mHealth interventions for non-communicable disease management in low- and middle-income countries found limited evidence of effectiveness, with interventions generally narrow in focus and dominated by text messaging for patients [6]. This has led to speculation that the limited impact of mHealth innovations may relate to a tendency to focus on single health system domains [7].

In Indonesia, a lower-middle income country by World Bank classification, ischemic heart disease and cerebrovascular disease are the two leading causes of disability-adjusted life years lost, with CVD estimated to be the cause of one-third of all deaths in 2016 [8]. Existing data suggest that less than one-third of Indonesians with moderate-to-high CVD risk receive any preventive care [9]. Current government policy responses articulate a strategy for preventing and managing CVD through advocacy, health promotion and health system strengthening [10]. As the health system is highly decentralised, local district health agencies are pivotal in implementing these policies. The agencies are responsible for healthcare delivery by nurses and community healthcare workers at neighborhood and village-level health centers, and by doctors at sub-district level primary healthcare centres. To strengthen primary healthcare, the government is also currently implementing a comprehensive eHealth platform.

This policy and emerging eHealth environment provides an opportunity to develop innovative technology-enabled primary healthcare interventions with potential for implementation at scale. Building on work in Australia, China and India [11-13], with a common component of clinical decision support but variation in disease focus and health system integration, we adapted SMART*health* (Systematic Medical Appraisal Referral and Treatment), a mobile technology-supported, multifaceted primary healthcare intervention aimed at improving the provision of guideline-based assessment and management of CVD risk, to the Malang district of East Java, Indonesia. We hypothesized that, compared to usual care, this intervention would be associated with greater appropriate preventive medication use and lower blood pressure levels among individuals at high CVD risk.

Methods

Study design

Details of the SMART*health* intervention are outlined in eAppendix 1 in Supplement 1. In brief, the intervention enabled neighborhood-based non-physician community healthcare workers (*kaders* in the Indonesian context), nurses at the village health centers and doctors at the primary healthcare centers to assess CVD risk using basic equipment and a clinical decision support application on a mobile tablet device. The application allowed *kaders* to collect essential information, inform an individual of their risk status, provide lifestyle advice, and refer high-risk individuals for nurse or physician consultation. High predicted risk was defined by the presence of: (1) a past history of CVD confirmed by a doctor; or (2) an extreme blood pressure elevation (systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg); or (3) a 10-year predicted CVD risk ≥ 30%; or (4) a 10-year predicted CVD risk of 20-29% and a systolic blood pressure >140 mmHg. In the absence of Indonesian

risk prediction charts, the 10-year risk of fatal or major non-fatal major CVD event was estimated using algorithms based on the World Health Organization/International Society of Hypertension "low information" risk charts tailored to the South-East Asian Region-B, which recommends screening individuals aged ≥40 years using age, sex, blood pressure, smoking and diabetes status [14]. Shared electronic record functionality allowed synchronous or asynchronous capture of patient data that were securely sent to and accessed from a central server. Doctors (on monthly visits to village health centers) and nurses also used a mobile application to receive tailored decision support around appropriate prescription of preventive medications, utilizing previous data collected by the *kaders* as well as new data collected during patient consultations. Treatment plans were immediately available to *kaders* ensuring community-based follow-up. An automated system alerted high-risk individuals by text message or interactive voice response to attend follow-up visits with healthcare providers and provided reminders promoting medication adherence. Community-wide health promotion, training, performance management and activity-based remuneration of healthcare workers, and support of essential medication procurement underpinned this system of care. Prior to finalizing the intervention, a health systems assessment was undertaken with district health authorities. This assessment, using an adapted Rapid Assessment Protocol for Insulin Access tool [15], helped contextualize the previously developed for SMART*health* theory-based logic model and modify the components as required (eFigure 1, Supplement 1). Logic model development and subsequent intervention modifications were guided by Michie's Behaviour Change Wheel that seeks to influence capability, opportunity and motivation to support behaviour change [16].

From September 2016 to March 2018, we performed a controlled quasi-experimental study of this complex primary care intervention in four intervention and four control villages in the

Malang district of East Java, Indonesia. Because the intervention was delivered through the existing healthcare infrastructure, close involvement of the district health authority, healthcare providers and community members in co-production and implementation was crucial. After detailed consultation, the strong preference of local partners was to identify villages for intervention where resources could be most easily accessed and adapted for timely implementation. Consequently, random selection of villages for the intervention was deemed infeasible. The Malang District Health Agency selected four villages from four primary healthcare centers to maximize feasibility and geographic and socioeconomic diversity. To be eligible, each primary healthcare center had to have at least one doctor, and each village health centre had to have at least one nurse regularly providing services and willing to participate in SMART*health* implementation. Four control villages were subsequently chosen. Each control village was matched to an intervention village based on population size, rurality, predominant occupation, distance from tobacco factories, and number of *kaders*. As an adequately matched control village could not be identified in the catchment area in the case of one primary healthcare center, a control village from a neighboring primary health center catchment area was selected (eFigure 2, Supplement 1).

The study received ethics approval from the Ethical Committee, Ministry of Research, Technology, and Higher Education, Medical Faculty of Brawijaya University (330/EC/KEPK/08/2016) and was registered on the Clinical Trial Registry of India (CTRI/2017/08/009387). Written informed consent was obtained from all participants who contributed data for analysis.

Procedures

In all eight villages, field researchers undertook a full census of adults aged ≥40 years through household visits between September 2016 and March 2017. This census constituted baseline data collected using identical equipment, procedures and criteria as used by *kaders* in the intervention villages (eAppendix 1, Supplement 1). Independent assessors re-evaluated villages between February 2018 and March 2018. Primary evaluation of intervention was based on researcher-identified high-risk individuals in the intervention villages, compared with researcher-identified high-risk individuals in the control villages. Due to anticipated discordance between researcher and *kader*-identified high-risk individuals in the intervention villages (eTable 1, Supplement 1), pre-specified sensitivity analyses were based on *kader*-identified high-risk patients (Supplement 2). To reduce the risk of ascertainment bias, field researchers were provided with lists of high-risk patients for follow-up in all villages but were not advised of the village allocation status.

Outcomes

The primary outcome was the proportion of high-risk individuals using appropriate preventive medications at follow-up. This was defined as self-reported use of at least one blood pressure lowering drug and statin for people at high risk without prior doctor-diagnosed CVD; or self-reported use of at least one blood pressure lowering drug, statin and an antiplatelet agent (unless concomitant anticoagulant use) for people with established CVD. Secondary outcomes were the proportion of high-risk individuals achieving a systolic blood pressure target of <140 mmHg and the mean change in systolic and diastolic blood pressure levels from baseline to end of follow-up among high-risk individuals. For the intervention villages, reporting of proportions of high-risk individuals referred by *kaders* to nurses or doctors, and of high-risk individuals receiving at least one follow-up visit by a *kader* was pre-specified.

202

203 ***Statistical analysis***

204 Eight villages allocated equally to intervention and control were estimated to provide 80%
205 power with a two-sided α=0.05 to detect an absolute difference of 18% in the proportion of
206 high-risk people on appropriate preventive medications, assuming a baseline rate of 10%,
207 cluster size of 144 individuals, and an intra-class correlation coefficient of 0.05.

208

209 Baseline characteristics of high-risk individuals were compared using chi-square and t-tests
210 as appropriate, with computation of standardized differences [17]. The associations between
211 the intervention and dichotomous outcomes were tested using modified Poisson models that
212 utilized a robust variance estimator with generalized estimating equations to estimate the
213 adjusted relative risk and 95% CI [18]. Binomial models were used to estimate the adjusted
214 risk difference with its 95% CI. Linear mixed models were used to report adjusted mean
215 differences (with 95% CI) for continuous outcomes. For all outcomes, to account for
216 correlations between participants from the same village, generalized estimating equations
217 with an exchangeable correlation structure that assumes all pairs of observations from the
218 same village have a common correlation were used.

219

220 All models adjusted for baseline values of the outcome as well as baseline covariates with a
221 between-group standardized difference $\geq$0.1 (with the exception of avoiding adjusting for
222 baseline use of individual component drug modalities for the outcome of appropriate
223 medication use, and vice versa). For all outcomes, we performed *post-hoc* sensitivity analyses
224 adjusting for no covariates and for all baseline covariates.

225

In additional *post hoc* analyses, the homogeneity of associations across subgroups on the primary outcome was tested by adding interaction terms to each model. Subgroups using baseline characteristics included age (above and below median at baseline), sex, diabetes, current smoking, education (primary school or less, some high school, more than high school), high-risk group type, and systolic blood pressure (above and below median at baseline).

All statistical significance tests were conducted using a 2-sided type 1 error rate of 5%. For secondary outcomes, adjustment for testing multiplicity employed a sequential Holm-Bonferroni method using a family size of three where all secondary outcomes are considered as part of the same family [19]. As fewer than 2% of primary and secondary outcome variables were missing, no imputation methods were used. Sample size was calculated using PASS 16 (NCSS, LLC, Kaysville, Utah). All analyses were conducted using SAS Enterprise Guide version 7.15 (SAS Institute Inc, Cary, North Carolina). Details for computing standardized differences, adjusting for testing multiplicity and calculating intraclass correlation coefficients are provided in eAppendix 2, Supplement 1).

Results

Baseline data collection commenced in September 2016, with follow-up data collection completed in March 2018. In total, 22,635 adults aged ≥40 years were identified (11,647 in the intervention villages and 10,988 in the control villages) (Figure 1, eTable 2 in Supplement 1). In the intervention villages, 3494 (29.9%) were identified as being at high CVD risk, compared to 3085 (28.1%) in the control villages. The follow-up rate of high-risk individuals was 77% overall and similar between control and intervention villages. Participants who were lost to follow-up appeared to be at higher CVD risk than those who were followed, although

baseline blood pressure and treatment rates were similar (eTable 3, Supplement 1). The median period from identification of high-risk status to follow-up assessment was 12.6 (interquartile range, IQR: 12.2, 13.1) months for control villages. This was shorter than the corresponding period for intervention villages (18.0, IQR: 17.5, 18.5 months), but similar to the period between intervention initiation and end of follow-up (11.5, IQR: 10.9, 12.2 months). This difference is explained by the need to deploy a limited number of field researchers to perform complete baseline assessments sequentially, commencing first in intervention villages, followed by control villages.

Table 1 – Baseline characteristics of the high-risk population

Characteristic	Control (n=3085)	Intervention (n=3494)	*P* value	Standardized difference
Age, mean (SD), y	59.0 (11.5)	58.3 (10.9)	.02	.06
Females, No. (%)	1838/3085 (59.6%)	2166/3494 (62.0%)	.07	.03
Education, No. (%)				
Primary school or less	2136/3085 (69.2%)	2139/3491 (61.3%)		
Some high school	791/3085 (25.6%)	1153/3491 (33.0%)	<.001	.17
More than high school	158/3085 (5.1%)	199/3491 (5.7%)		
Diabetes, No. (%)	247/3085 (8.0%)	344/3494 (9.8%)	.009	.06
Current smoking, No. (%)	595/3085 (19.3%)	633/3494 (18.1%)	.22	.03
Systolic blood pressure, mean (SD), mmHg	167.3 (21.3)	166.6 (22.2)	.20	.03
Diastolic blood pressure, mean (SD), mmHg	101.3 (13.1)	101.1 (13.7)	.40	.02
Body mass index, mean (SD), kg/m^2	25.7 (4.8)	26.0 (4.8)	.006	.06
High risk due to known cardiovascular disease, No. (%)	499/3085 (16.2%)	729/3494 (20.9%)	<.001	.12
High risk due to other reasons, No. (%)	2586/3085 (83.3%)	2765/3494 (79.1%)	<.001	.12

On appropriate preventive medications[a], No. (%)	2/3085 (0.1%)	28/3494 (0.8%)	<.001	.11
On blood pressure lowering medication(s), No. (%)	304/3085 (9.9%)	484/3494 (13.9%)	<.001	.12
On statin therapy, No. (%)	21/3085 (0.7%)	75/3494 (2.1%)	.001	.12
On antiplatelet medication(s)[b], No. (%)	13/499 (2.6%)	47/729 (6.4%)	0.002	.18

Abbreviations: SD, standard deviation.

[a]Combination of blood pressure lowering medication, statin therapy and antiplatelet medication if high risk due to known cardiovascular disease; combination of BP lowering medication(s) and statin therapy if high risk due to other reasons.

[b]Among individuals at high risk due to known cardiovascular disease. Missing values – body mass index (63 control, 56 intervention); blood pressure (5 control, 8 intervention). The missing blood pressure values were due to data transmission errors from the mobile application to the central database, as there were no missing values for determining high-risk status (the automatic calculation of which requires blood pressure values for those without known cardiovascular disease).

In the intervention villages, *kaders* screened 86.4% of the census population through household visits, identifying 20.9% (2301 individuals) as being at high CVD risk. There was discordance between researcher- and *kader*-identified high-risk individuals (eTable 1, Supplement 1), anticipated as a result of visit-to-visit BP variability including regression to the mean. All high-risk individuals identified by *kaders* were referred for further care. Of these, 1060 (46.0%) only visited a public sector nurse or a doctor involved with SMART*health*, 278 (12.1%) only consulted a private sector health practitioner and 161 (7.0%) visited both types of provider on at least one occasion. A total of 2101 (91.3%) high-risk individuals had at least one subsequent follow-up *kader*. The distribution of follow-up by *kaders* (Figure 3) indicates an overall median period of 9.2 months (IQR: 7.2, 10.3) with 33%, 39% and 22% having 1, 2 and 3 clinical interactions over this period, respectively.

At the end of follow-up, 15.5% of researcher-identified high-risk individuals in intervention villages were taking appropriate preventive treatment, compared with 1.0% of their control

287 villages counterparts (adjusted RR, 14.8 [95% CI, 6.6 to 33.2]; risk difference, 14.1% [95%
288 CI, 12.7% to 15.6%]) (Table 2). This difference was particularly driven by increased use of
289 blood pressure lowering medication (56.8% vs. 15.7%; adjusted RR, 3.6 [95% CI, 2.5 to 5.4;
290 risk difference, 39.4% [95% CI, 37.0% to 41.7%]). Significant differences were observed for
291 statin use, but was borderline non-significant for antiplatelet medication use among those
292 with established CVD. Similar results were obtained with no or full covariate adjustment
293 (eTable 5, Supplement 1).
294

295 **Table 2 – Intervention effects – primary analysis based on researcher-identified high-**
296 **risk individuals in control and intervention villages.**

Outcome	Control (n=2429)	Intervention (n=2632)	Adjusted risk difference (95% CI)	Adjusted relative risk or mean difference (95% CI)	*P*[d]	ICC
Appropriate treatment[a], No. (%)	25/2429 (1.0%)	409/2632 (15·5%)	14.1% (12.7 to 15.6)	14.8 (6.6 to 33.2)	<.001	.073
Achieving BP target, No. (%)	539/2429 (22.2%)	815/2632 (31·0%)	7.6% (5.4 to 9.9)	1.3 (1.2 to 1.5)	<.001	<.001
Change in SBP, mean (SEM), mmHg	-9.2 (0.4)	-17·2 (0·4)	–	-8.3 (-10.1 to -6.6)	<.001	.002
Change in DBP, mean (SEM), mmHg	-5.0 (0.2)	-8·3 (0·2)	–	-3.6 (-4.5 to -2.6)	<.001	.001
BP lowering medication, No. (%)	382/2429 (15.7%)	1495/2632 (56·8%)	39.4% (37.0 to 41.7)	3.6 (2.5 to 5.4)	<.001	.022
Lipid lowering medication, No. (%)	59/2429 (2.4%)	523/2632 (19·9%)	16.7% (15.1 to 18.3)	9.3 (3.7 to 23.2)	<.001	.106
Antiplatelet medication, No. (%)[b]	47/371 (12.7%)	128/520 (24·6%)	9.9% (5.0 to 14.8)	1.9 (1.0 to 3.8)	.06	.051
Current smoking[c], No. (%)	447/2429 (18.4%)	420/2632 (16·0%)	-	-	-	-
Change in BMI, mean (SEM), kg/m^2	0.0 (0.1)	-0·3 (0·1)	–	-0.2 (-0.9 to 0.4)	.49	.020

297 Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval; CVD,
298 cardiovascular disease; DBP, diastolic blood pressure; ICC, intra-class correlation
299 coefficient; SEM, standard error of the mean.

For each outcome (other than the outcomes of use of individual drug modalities), the model was adjusted for baseline value of the outcome as well as baseline covariates with a between-group standardized difference ≥0.1, i.e. baseline education, baseline appropriate medication use and baseline high-risk category (but not baseline use of individual drug modalities [BP lowering medication, lipid lowering medication, antiplatelet medication] because of the inclusion of baseline appropriate medication use). For each of the outcomes of use of individual drug modalities, the model was adjusted for the baseline value of the outcome, baseline education and baseline high-risk category (but not baseline appropriate medication use because of the inclusion of the baseline value of the individual drug modality).
[a]Combination of BP lowering medication(s), statin therapy and antiplatelet medication if high risk due to known CVD; combination of BP lowering medication(s) and statin therapy if high risk of CVD events due to other reasons.
[b]Among individuals at high risk due to known CVD at baseline.
[c]Model does not converge with inclusion of any covariates.
[d]P-value for adjusted relative risk or mean difference.
Missing values – body mass index (63 control, 50 intervention); blood pressure (3 control, 9 intervention). The missing blood pressure values were due to data transmission errors from the mobile application to the central database, as there were no missing values for determining high-risk status (the automatic calculation of which requires blood pressure values for those without known cardiovascular disease).

A greater proportion of high-risk individuals in intervention villages achieved a systolic blood pressure target of <140 mmHg at the end of follow-up, compared with those in control villages (31.0% vs. 22.2%; adjusted RR, 1.3 [95% CI, 1.2 to 1.5]; risk difference, 7.6%, [95% CI, 5.4% to 9.9%]). At the end of follow-up, the mean (SD) systolic blood pressure reduction from baseline was 17.2 (22.4) mmHg and 9.2 (20.3) mmHg, respectively, among high-risk individuals in the intervention and control villages (adjusted mean difference, -8.3 mmHg [95% CI, -10.1 to -6.6 mmHg]). Similarly, diastolic blood pressure was significantly more reduced among high-risk individuals in the intervention compared to control villages (adjusted mean difference, -3.6 mmHg [95% CI, -4.5 to -2.6 mmHg). Sensitivity analyses based on *kader*-identified high-risk individuals in the intervention villages showed stronger associations between the intervention and treatment outcomes, compared to the primary analysis based on researcher-identified high-risk individuals (Table 3). In all analyses, there were no significant between-group differences in self-reported current smoking and measured body mass index at the end of follow-up.

Table 3 – Intervention effects - sensitivity analyses based on *kader*-identified high-risk individuals in the intervention villages.

Outcome	Control (n=2429)	Intervention (n=1894)	Adjusted risk difference (95% CI)	Adjusted relative risk or mean difference (95% CI)	P-value[d]	ICC
Appropriate treatment[a], No. (%)	25/2429 (1.0%)	482/1894 (25.4%)	23.9% (21.8 to 25.9)	24.4 (11.1 to 53.3)	<.001	0.068
Achieving BP target, No. (%)	539/2429 (22.2%)	677/1894 (35.7%)	9.8% (7.3 to 12.2)	1.4 (1.3 to 1.6)	<.001	<.001
Change in SBP, mean (SEM), mmHg	-9.2 (0.4)	-16.6 (0.5)	−	-8.7 (-10.1 to -7.4)	<.001	0.001
Change in DBP, mean (SEM), mmHg	-5.0 (0.2)	-7.9 (0.3)	−	-3.5 (-4.5 to -2.5)	<.001	0.002
BP lowering medication, No. (%)	382/2429 (15.7%)	1483/1894 (78.3%)	60.9% (58.4 to 63.3)	5.1 (3.4 to 7.5)	<.001	0.022
Lipid lowering medication, No. (%)	59/2429 (2.4%)	590/1894 (31.2%)	28.0% (25.8 to 30.2)	15.4 (5.9 to 39.8)	<.001	0.114
Antiplatelet medication[b], No. (%)	47/371 (12.7%)	99/301 (32.9%)	18.0% (11.4 to 24.5)	2.6 (1.3 to 5.4)	0.01	0.059
Current smoking[c], No. (%)	447/2429 (18.4%)	315/1894 (16.6%)	-3.0% (-5.2 to -0.8)	0.9 (0.7 to 1.2)	0.63	0.006
Change in BMI, mean (SEM), kg/m^2	0.0 (0.1)	-0.1 (0.1)	−	-0.1 (-0.8 to 0.5)	0.63	0.016

Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease; DBP, diastolic blood pressure; ICC, intra-class correlation coefficient; SEM, standard error of the mean

For each outcome, the model was adjusted for baseline value of the outcome as well as baseline covariates with a between-group standardized difference ≥0.1, i.e. baseline age, baseline education, baseline systolic and diastolic blood pressure and baseline body mass index.

[a]Combination of BP lowering medication(s), statin therapy and antiplatelet medication if high risk due to known CVD; combination of BP lowering medication(s) and statin therapy if high risk of CVD events due to other reasons.

[b]Among individuals at high risk due to known CVD at baseline.

[c]Adjusted on all baseline covariates with a standardised difference > 0.1, except for current smoking at baseline which had to be removed from the model due to lack of convergence.

[d]P-value for adjusted relative risk or mean difference.
Missing values – body mass index (63 control, 30 intervention); blood pressure (3 control, 26 intervention). The missing blood pressure values were due to data transmission errors from the mobile application to the central database, as there were no missing values for determining high-risk status (the automatic calculation of which requires blood pressure values for those without known cardiovascular disease).

Post-hoc subgroup analyses suggest that the associations between the intervention and the primary outcome were smaller among individuals with higher educational attainment, prior diagnosed CVD and diabetes (all p for homogeneity ≤0.05) (eFigure 3, Supplement 1).

Discussion

This study showed that a mobile technology-supported, multi-faceted primary healthcare intervention was associated with greater use of appropriate preventive CVD medications among high-risk individuals in a rural Indonesian community. The intervention was particularly associated with increased use of blood pressure lowering medications and reductions in blood pressure levels. The more modest association with improvement in achieving blood pressure target reflects the very high baseline blood pressure levels in this population.

Mobile technology-driven solutions can potentially improve the quality and efficiency of primary healthcare services for CVD prevention in resource-constrained environments. However, the few interventions that have undergone controlled evaluation have been shown to have modest, if any, effects [6, 8, 20]. Much focus has been on technology, with insufficient attention on applying a multi-domain health systems integration framework to development and implementation [21]. The intervention evaluated in this study was developed using a theory-informed approach complemented by local health system contextualization. As a consequence the intervention was complex, addressing barriers in

multiple health system domains. While the complex nature of intervention might be a critical contributor to improved outcomes, this inevitably leads to uncertainty about the relative contribution of each component. This will be further evaluated through a detailed process evaluation [22].

A number of features of the Indonesian health system likely facilitated implementation of the intervention. First, senior district health agency officials were engaged in the context of a supportive policy environment. As a consequence of continuous data collection through the SMART*health* platform, it was recognised early that prior district-level procurement of essential CVD preventive medications, whilst affordable within typical procurement budgets, would be inadequate to meet demand. While the short-term acquisition of additional medication was supported by study funding (finally supporting ~50% of prescribed medications), existing purchasing and supply chain processes that avoided stock-outs was critical.

Second, workforce characteristics in rural Indonesia enabled implementation. A core element of the theory of change was to generate community-level demand at the household level, rather than relying on promoting healthcare seeking behaviour among largely asymptomatic individuals. The presence of a community healthcare workforce already delivering care through household visits provided task-sharing opportunities through workflow modification, avoiding the need for an entirely new cadre of workers [23, 24].

Third, task-sharing was strongly facilitated by the ability of the district health agency to authorize subsequent prescription of essential medications by nurses, with ongoing delegation where appropriate by physicians. The importance of nurse-based prescribing has been

404 highlighted elsewhere [25, 26]. The positive associations between the intervention and
405 outcomes were observed despite follow-up encompassing both public and private sector
406 prescribers in this environment, as typically seen in many low- and middle-income countries.
407 The latter were not utilizing the intervention, which reinforces the important central role that
408 community healthcare workers may play in ensuring integration and continuity of care.
409
410 A key limitation of the study was non-random allocation of the villages to intervention or
411 control, which likely introduced selection bias. Despite attempts to match villages, high-risk
412 individuals in the intervention villages were more educated and had higher baseline treatment
413 rates than those in the control villages. We tried to account for this in our analyses by
414 controlling for observed differences in baseline characteristics. However, residual
415 confounding remains a possibility, although this would need to be very substantial to change
416 the overall conclusions, given the magnitude of the associations observed [27]. There was
417 anticipated discordance between researcher- and *kader*-identified high risk individuals in the
418 intervention villages, which was the rationale for a pre-specified sensitivity analysis using
419 data from *kader*-identified high-risk individuals. This discordance was largely driven by
420 within-person differences in recorded blood pressure at levels consistent with previously
421 reported regression to the mean and visit-to-visit blood pressure variability in people with
422 hypertension at levels observed in this population [28, 29]. As a consequence, a large
423 proportion of researcher-identified high-risk individuals would not have had an opportunity
424 to be exposed to the intervention during the follow-up period. Thus, the primary analyses
425 presented likely represent a more conservative assessment of associations. Conversely, the
426 higher risk profile of participants who were not followed-up, compared to those who were
427 reassessed, may have resulted in over-estimation of the true associations.
428

There are additional potential limitations to consider. The performance of the risk charts in this population overall and in certain subgroups is uncertain, however this would not introduce bias in the between-group comparisons. Self-report was used for medication use, although the pre-specified secondary outcome of blood pressure provides some objective verification. Another concern may be that the study was not powered to identify effects on clinical events. However in the context of using drugs of proven efficacy and safety, blood pressure would be considered an appropriate surrogate for CVD events [30]. Additionally, it is possible that community members from intervention villages may have disclosed prior exposure to the SMART*health* program to field researchers during follow-up, impacting on blinded outcome assessment. We were unable to assess the extent to which this may have occurred. A further potential limitation is that control villages were selected from sub-districts served by the same primary healthcare center as the intervention villages, providing a theoretical basis for contamination. In practice, very few patients currently seek and/or receive CVD care at the primary healthcare center level. In addition, if there were any contamination due to SMART*health*-exposed doctors treating control village community members, this would bias the results towards the null. Finally, the small number and selected nature of the villages included limits the generalizability of the findings.

While the results are encouraging, further research is important to facilitate and demonstrate scalability and sustainability [31]. Relevant data will emerge from the economic and process evaluations from this study; however, institutionalizing such interventions needs to address a range of issues for effective health system integration. These include ensuring interoperability with Indonesia's emerging eHealth strategy and infrastructure, drug and equipment supply chains, workforce and management training, and alignment with existing healthcare financing, social insurance and reimbursement mechanisms. Finally, it will be necessary to

broaden the disease focus to provide comprehensive primary healthcare services for a range of common conditions for ultimate sustainability and maximum impact.

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Author Contributions

Drs Patel and Praveen had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflict of Interest Disclosures

The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Patel, Dr Praveen and Mr Pilard report that their employer's wholly-owned social enterprise, George Health Enterprises, has commercial relationships involving digital health innovations. All other authors do not have any potential conflicts of interest to declare. No other disclosures were reported.

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David Peiris (PhD) and Chetan Purad (MBBS) provided advice and input into the design and execution of this study; Laurent Billot (MSc) provided advice on statistical methodology. Dr Peiris, Dr Purad and Mr Billot were employees of The George Institute for Global Health during the study, but did not receive any additional compensation for their contributions. M.

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Figure legends

Figure 1: Flowchart of participants through the study

Figure 2: Distribution of follow-up visits by *kaders*

Online supplements

Supplement 1

eAppendix1: SMART*health* program in Indonesia

eAppendix 2: Additional details on statistical methods

eFigure 1: SMART*health* logic model

eFigure 2: Study villages

eTable 1: Concordance between *kader*-identified and researcher-identified high-risk individuals in the intervention villages

eTable 2: Baseline characteristics of the census population

eTable 3: Baseline characteristics of high-risk individuals who were and were not followed-up

eTable 4: Additional baseline characteristics of high-risk individuals

eTable 5: Intervention effects – primary analysis with full adjustment for baseline covariates

eFigure 3: Subgroup analyses for primary outcome

Supplement 2

Statistical Analysis Plan and deviations

Supplement 3

TIDieR Checklist