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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1 **Effect of a multifaceted mobile technology enabled primary care intervention on**

2 **cardiovascular disease risk management in rural Indonesia: a quasi-experimental study**

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

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29 **Key points (75-100 words)**

30 **Question:** Is a mobile technology-supported primary healthcare intervention associated with

31 greater use of preventive drug treatments compared to usual care among individuals at high

32 cardiovascular disease risk?

33 **Findings:** In this quasi-experimental study involving 8 villages and 6579 high-risk people in

34 rural Indonesia, 15.5% of individuals in the intervention villages reported use of appropriate

35 use of preventive medications compared with 1.0% in the control villages. The difference in

36 blood pressure lowering drug use was 57% vs. 16%.

37 **Meaning:** The primary healthcare intervention was associated with increased use of

38 preventive drug therapies in people with high predicted cardiovascular disease risk.

39 (98 words)

40

Abstract

41

42 **Importance:** Cardiovascular diseases (CVD) are the leading cause of disease burden in

43 Indonesia. Implementation of effective interventions for CVD prevention is limited.

44 **Objective:** To evaluate whether a mobile technology-supported primary healthcare

45 intervention would improve use of preventive drug treatment among people with high CVD

46 risk, vs usual care.

47 **Design:** Quasi-experimental study involving four intervention and four control villages

48 conducted between September 2016 and March 2018. Median duration of follow-up was 12.2

49 months.

50 **Setting:** Malang district, Indonesia

51 **Participants:** Residents aged ≥40 years were invited to participate. Those with high

52 predicted 10-year CVD risk (previous diagnosed CVD; systolic blood pressure (BP) >160

53 mmHg or diastolic BP >100 mmHg; 10-year predicted CVD risk ≥ 30%; or 10-year predicted

54 CVD risk of 20-29% and a systolic BP>140 mmHg) were followed.

55 **Intervention:** A multi-faceted mobile technology-supported intervention facilitating

56 community-based CVD risk screening with referral, tailored clinical decision support for

57 drug prescription and patient follow-up.

58 **Main outcomes and measures:** The primary outcome was the proportion on appropriate

59 preventive CVD medications, defined as at least one BP lowering drug and a statin for all

60 high-risk individuals, and an antiplatelet drug for those with prior diagnosed CVD.

61 Secondary outcomes included mean change in BP from baseline.

62 **Results:** Among 22,635 adults, 3494 (29.9%) and 3085 (28.1%) had high predicted CVD risk

63 in the intervention and control villages, respectively. Of these, follow-up was completed in

64 2632 (75.3%) from intervention villages and 2429 (78.7%) from control villages. At follow-

65 up, 15.5% of high-risk individuals in intervention villages were taking appropriate preventive

66 CVD medications, compared with 1.0% of in control villages (adjusted risk difference,

67 14.1%, [95% CI, 12.7% to 15.6%]). This difference was driven by higher BP lowering

68 treatment use (56.8% vs. 15.7%; adjusted risk difference, 39.4% [95% CI, 37.0% to 41.7%).

69 The adjusted mean difference in change in systolic BP from baseline was -8.3 mmHg, [95%

70 CI, -6.6 to -10.1 mmHg]).

71 **Conclusions and relevance:** A multi-faceted mobile technology supported primary

72 healthcare intervention was associated with greater use of preventive CVD medication use

73 and lower BP levels among high-risk individuals in a rural Indonesian population.

74

75 **Clinical Trial Registration**

76 Clinical Trial Registry of India,

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

78 WORD COUNT: 342

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.

6

103

104   This policy and emerging eHealth environment provides an opportunity to develop

105   innovative technology-enabled primary healthcare interventions with potential for

106   implementation at scale. Building on work in Australia, China and India [11-13], with a

107   common component of clinical decision support but variation in disease focus and health

108   system integration, we adapted SMART*health* (Systematic Medical Appraisal Referral and

109   Treatment), a mobile technology-supported, multifaceted primary healthcare intervention

110   aimed at improving the provision of guideline-based assessment and management of CVD

111   risk, to the Malang district of East Java, Indonesia. We hypothesized that, compared to usual

112   care, this intervention would be associated with greater appropriate preventive medication use

113   and lower blood pressure levels among individuals at high CVD risk.

114

115   **Methods**

116   *Study design*

117   Details of the SMART*health* intervention are outlined in eAppendix 1 in Supplement 1. In

118   brief, the intervention enabled neighborhood-based non-physician community healthcare

119   workers (*kaders* in the Indonesian context), nurses at the village health centers and doctors at

120   the primary healthcare centers to assess CVD risk using basic equipment and a clinical

121   decision support application on a mobile tablet device. The application allowed *kaders* to

122   collect essential information, inform an individual of their risk status, provide lifestyle

123   advice, and refer high-risk individuals for nurse or physician consultation. High predicted risk

124   was defined by the presence of: (1) a past history of CVD confirmed by a doctor; or (2) an

125   extreme blood pressure elevation (systolic blood pressure >160 mmHg or diastolic blood

126   pressure >100 mmHg); or (3) a 10-year predicted CVD risk $\geq$ 30%; or (4) a 10-year predicted

127   CVD risk of 20-29% and a systolic blood pressure >140 mmHg. In the absence of Indonesian

128   risk prediction charts, the 10-year risk of fatal or major non-fatal major CVD event was

129   estimated using algorithms based on the World Health Organization/International Society of

130   Hypertension "low information" risk charts tailored to the South-East Asian Region-B, which

131   recommends screening individuals aged ≥40 years using age, sex, blood pressure, smoking

132   and diabetes status [14]. Shared electronic record functionality allowed synchronous or

133   asynchronous capture of patient data that were securely sent to and accessed from a central

134   server. Doctors (on monthly visits to village health centers) and nurses also used a mobile

135   application to receive tailored decision support around appropriate prescription of preventive

136   medications, utilizing previous data collected by the *kaders* as well as new data collected

137   during patient consultations. Treatment plans were immediately available to *kaders* ensuring

138   community-based follow-up. An automated system alerted high-risk individuals by text

139   message or interactive voice response to attend follow-up visits with healthcare providers and

140   provided reminders promoting medication adherence. Community-wide health promotion,

141   training, performance management and activity-based remuneration of healthcare workers,

142   and support of essential medication procurement underpinned this system of care. Prior to

143   finalizing the intervention, a health systems assessment was undertaken with district health

144   authorities. This assessment, using an adapted Rapid Assessment Protocol for Insulin Access

145   tool [15], helped contextualize the previously developed for SMART*health* theory-based

146   logic model and modify the components as required (eFigure 1, Supplement 1). Logic model

147   development and subsequent intervention modifications were guided by Michie's Behaviour

148   Change Wheel that seeks to influence capability, opportunity and motivation to support

149   behaviour change [16].

150

151   From September 2016 to March 2018, we performed a controlled quasi-experimental study of

152   this complex primary care intervention in four intervention and four control villages in the

153 Malang district of East Java, Indonesia. Because the intervention was delivered through the

154 existing healthcare infrastructure, close involvement of the district health authority,

155 healthcare providers and community members in co-production and implementation was

156 crucial. After detailed consultation, the strong preference of local partners was to identify

157 villages for intervention where resources could be most easily accessed and adapted for

158 timely implementation. Consequently, random selection of villages for the intervention was

159 deemed infeasible. The Malang District Health Agency selected four villages from four

160 primary healthcare centers to maximize feasibility and geographic and socioeconomic

161 diversity. To be eligible, each primary healthcare center had to have at least one doctor, and

162 each village health centre had to have at least one nurse regularly providing services and

163 willing to participate in SMART*health* implementation. Four control villages were

164 subsequently chosen. Each control village was matched to an intervention village based on

165 population size, rurality, predominant occupation, distance from tobacco factories, and

166 number of *kaders*. As an adequately matched control village could not be identified in the

167 catchment area in the case of one primary healthcare center, a control village from a

168 neighboring primary health center catchment area was selected (eFigure 2, Supplement 1).

169

170 The study received ethics approval from the Ethical Committee, Ministry of Research,

171 Technology, and Higher Education, Medical Faculty of Brawijaya University

172 (330/EC/KEPK/08/2016) and was registered on the Clinical Trial Registry of India

173 (CTRI/2017/08/009387). Written informed consent was obtained from all participants who

174 contributed data for analysis.

175

176 ***Procedures***

177   In all eight villages, field researchers undertook a full census of adults aged ≥40 years

178   through household visits between September 2016 and March 2017. This census constituted

179   baseline data collected using identical equipment, procedures and criteria as used by *kaders*

180   in the intervention villages (eAppendix 1, Supplement 1). Independent assessors re-evaluated

181   villages between February 2018 and March 2018. Primary evaluation of intervention was

182   based on researcher-identified high-risk individuals in the intervention villages, compared

183   with researcher-identified high-risk individuals in the control villages. Due to anticipated

184   discordance between researcher and *kader*-identified high-risk individuals in the intervention

185   villages (eTable 1, Supplement 1), pre-specified sensitivity analyses were based on *kader*-

186   identified high-risk patients (Supplement 2). To reduce the risk of ascertainment bias, field

187   researchers were provided with lists of high-risk patients for follow-up in all villages but

188   were not advised of the village allocation status.

189

190   ***Outcomes***

191   The primary outcome was the proportion of high-risk individuals using appropriate

192   preventive medications at follow-up. This was defined as self-reported use of at least one

193   blood pressure lowering drug and statin for people at high risk without prior doctor-

194   diagnosed CVD; or self-reported use of at least one blood pressure lowering drug, statin and

195   an antiplatelet agent (unless concomitant anticoagulant use) for people with established CVD.

196   Secondary outcomes were the proportion of high-risk individuals achieving a systolic blood

197   pressure target of <140 mmHg and the mean change in systolic and diastolic blood pressure

198   levels from baseline to end of follow-up among high-risk individuals. For the intervention

199   villages, reporting of proportions of high-risk individuals referred by *kaders* to nurses or

200   doctors, and of high-risk individuals receiving at least one follow-up visit by a *kader* was pre-

201   specified.

202

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 ≥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

226   In additional *post hoc* analyses, the homogeneity of associations across subgroups on the

227   primary outcome was tested by adding interaction terms to each model. Subgroups using

228   baseline characteristics included age (above and below median at baseline), sex, diabetes,

229   current smoking, education (primary school or less, some high school, more than high

230   school), high-risk group type, and systolic blood pressure (above and below median at

231   baseline).

232

233   All statistical significance tests were conducted using a 2-sided type 1 error rate of 5%. For

234   secondary outcomes, adjustment for testing multiplicity employed a sequential Holm-

235   Bonferroni method using a family size of three where all secondary outcomes are considered

236   as part of the same family [19]. As fewer than 2% of primary and secondary outcome

237   variables were missing, no imputation methods were used. Sample size was calculated using

238   PASS 16 (NCSS, LLC, Kaysville, Utah). All analyses were conducted using SAS Enterprise

239   Guide version 7.15 (SAS Institute Inc, Cary, North Carolina). Details for computing

240   standardized differences, adjusting for testing multiplicity and calculating intraclass

241   correlation coefficients are provided in eAppendix 2, Supplement 1).

242

243   **Results**

244   Baseline data collection commenced in September 2016, with follow-up data collection

245   completed in March 2018. In total, 22,635 adults aged ≥40 years were identified (11,647 in

246   the intervention villages and 10,988 in the control villages) (Figure 1, eTable 2 in Supplement

247   1). In the intervention villages, 3494 (29.9%) were identified as being at high CVD risk,

248   compared to 3085 (28.1%) in the control villages. The follow-up rate of high-risk individuals

249   was 77% overall and similar between control and intervention villages. Participants who were

250   lost to follow-up appeared to be at higher CVD risk than those who were followed, although

251　baseline blood pressure and treatment rates were similar (eTable 3, Supplement 1). The

252　median period from identification of high-risk status to follow-up assessment was 12.6

253　(interquartile range, IQR: 12.2, 13.1) months for control villages. This was shorter than the

254　corresponding period for intervention villages (18.0, IQR: 17.5, 18.5 months), but similar to

255　the period between intervention initiation and end of follow-up (11.5, IQR: 10.9, 12.2

256　months). This difference is explained by the need to deploy a limited number of field

257　researchers to perform complete baseline assessments sequentially, commencing first in

258　intervention villages, followed by control villages.

259

260　**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%)	<.001	.17
Some high school	791/3085 (25.6%)	1153/3491 (33.0%)		
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

261   Abbreviations: SD, standard deviation.

262   [a]Combination of blood pressure lowering medication, statin therapy and antiplatelet
263   medication if high risk due to known cardiovascular disease; combination of BP lowering
264   medication(s) and statin therapy if high risk due to other reasons.
265   [b]Among individuals at high risk due to known cardiovascular disease. Missing values – body
266   mass index (63 control, 56 intervention); blood pressure (5 control, 8 intervention). The
267   missing blood pressure values were due to data transmission errors from the mobile
268   application to the central database, as there were no missing values for determining high-risk
269   status (the automatic calculation of which requires blood pressure values for those without
270   known cardiovascular disease).

271

272

273   In the intervention villages, *kaders* screened 86.4% of the census population through

274   household visits, identifying 20.9% (2301 individuals) as being at high CVD risk. There was

275   discordance between researcher- and *kader*-identified high-risk individuals (eTable 1,

276   Supplement 1), anticipated as a result of visit-to-visit BP variability including regression to

277   the mean. All high-risk individuals identified by *kaders* were referred for further care. Of

278   these, 1060 (46.0%) only visited a public sector nurse or a doctor involved with

279   SMART*health*, 278 (12.1%) only consulted a private sector health practitioner and 161

280   (7.0%) visited both types of provider on at least one occasion. A total of 2101 (91.3%) high-

281   risk individuals had at least one subsequent follow-up *kader*. The distribution of follow-up by

282   *kaders* (Figure 3) indicates an overall median period of 9.2 months (IQR: 7.2, 10.3) with

283   33%, 39% and 22% having 1, 2 and 3 clinical interactions over this period, respectively.

284

285   At the end of follow-up, 15.5% of researcher-identified high-risk individuals in intervention

286   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.

300 For each outcome (other than the outcomes of use of individual drug modalities), the model
301 was adjusted for baseline value of the outcome as well as baseline covariates with a between-
302 group standardized difference ≥0.1, i.e. baseline education, baseline appropriate medication
303 use and baseline high-risk category (but not baseline use of individual drug modalities [BP
304 lowering medication, lipid lowering medication, antiplatelet medication] because of the
305 inclusion of baseline appropriate medication use). For each of the outcomes of use of
306 individual drug modalities, the model was adjusted for the baseline value of the outcome,
307 baseline education and baseline high-risk category (but not baseline appropriate medication
308 use because of the inclusion of the baseline value of the individual drug modality).
309 [a]Combination of BP lowering medication(s), statin therapy and antiplatelet medication if high
310 risk due to known CVD; combination of BP lowering medication(s) and statin therapy if high
311 risk of CVD events due to other reasons.
312 [b]Among individuals at high risk due to known CVD at baseline.
313 [c]Model does not converge with inclusion of any covariates.
314 [d]P-value for adjusted relative risk or mean difference.
315 Missing values – body mass index (63 control, 50 intervention); blood pressure (3 control, 9
316 intervention). The missing blood pressure values were due to data transmission errors from
317 the mobile application to the central database, as there were no missing values for
318 determining high-risk status (the automatic calculation of which requires blood pressure
319 values for those without known cardiovascular disease).
320

321 A greater proportion of high-risk individuals in intervention villages achieved a systolic

322 blood pressure target of <140 mmHg at the end of follow-up, compared with those in control

323 villages (31.0% vs. 22.2%; adjusted RR, 1.3 [95% CI, 1.2 to 1.5]; risk difference, 7.6%, [95%

324 CI, 5.4% to 9.9%]). At the end of follow-up, the mean (SD) systolic blood pressure reduction

325 from baseline was 17.2 (22.4) mmHg and 9.2 (20.3) mmHg, respectively, among high-risk

326 individuals in the intervention and control villages (adjusted mean difference, -8.3 mmHg

327 [95% CI, -10.1 to -6.6 mmHg]). Similarly, diastolic blood pressure was significantly more

328 reduced among high-risk individuals in the intervention compared to control villages

329 (adjusted mean difference, -3.6 mmHg [95% CI, -4.5 to -2.6 mmHg). Sensitivity analyses

330 based on *kader*-identified high-risk individuals in the intervention villages showed stronger

331 associations between the intervention and treatment outcomes, compared to the primary

332 analysis based on researcher-identified high-risk individuals (Table 3). In all analyses, there

333 were no significant between-group differences in self-reported current smoking and measured

334 body mass index at the end of follow-up.

335

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

338 Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval; CVD,
339 cardiovascular disease; DBP, diastolic blood pressure; ICC, intra-class correlation
340 coefficient; SEM, standard error of the mean
341 For each outcome, the model was adjusted for baseline value of the outcome as well as
342 baseline covariates with a between-group standardized difference ≥0.1, i.e. baseline age,
343 baseline education, baseline systolic and diastolic blood pressure and baseline body mass
344 index.
345 [a]Combination of BP lowering medication(s), statin therapy and antiplatelet medication if high
346 risk due to known CVD; combination of BP lowering medication(s) and statin therapy if high
347 risk of CVD events due to other reasons.
348 [b]Among individuals at high risk due to known CVD at baseline.
349 [c]Adjusted on all baseline covariates with a standardised difference > 0.1, except for current
350 smoking at baseline which had to be removed from the model due to lack of convergence.

351   dP-value for adjusted relative risk or mean difference.

352   Missing values – body mass index (63 control, 30 intervention); blood pressure (3 control, 26

353   intervention). The missing blood pressure values were due to data transmission errors from

354   the mobile application to the central database, as there were no missing values for

355   determining high-risk status (the automatic calculation of which requires blood pressure

356   values for those without known cardiovascular disease).

357

358   *Post-hoc* subgroup analyses suggest that the associations between the intervention and the

359   primary outcome were smaller among individuals with higher educational attainment, prior

360   diagnosed CVD and diabetes (all p for homogeneity ≤0.05) (eFigure 3, Supplement 1).

361

Discussion

363   This study showed that a mobile technology-supported, multi-faceted primary healthcare

364   intervention was associated with greater use of appropriate preventive CVD medications

365   among high-risk individuals in a rural Indonesian community. The intervention was

366   particularly associated with increased use of blood pressure lowering medications and

367   reductions in blood pressure levels. The more modest association with improvement in

368   achieving blood pressure target reflects the very high baseline blood pressure levels in this

369   population.

370

371   Mobile technology-driven solutions can potentially improve the quality and efficiency of

372   primary healthcare services for CVD prevention in resource-constrained environments.

373   However, the few interventions that have undergone controlled evaluation have been shown

374   to have modest, if any, effects [6, 8, 20]. Much focus has been on technology, with

375   insufficient attention on applying a multi-domain health systems integration framework to

376   development and implementation [21]. The intervention evaluated in this study was

377   developed using a theory-informed approach complemented by local health system

378   contextualization. As a consequence the intervention was complex, addressing barriers in

379   multiple health system domains. While the complex nature of intervention might be a critical

380   contributor to improved outcomes, this inevitably leads to uncertainty about the relative

381   contribution of each component. This will be further evaluated through a detailed process

382   evaluation [22].

383

384   A number of features of the Indonesian health system likely facilitated implementation of the

385   intervention. First, senior district health agency officials were engaged in the context of a

386   supportive policy environment. As a consequence of continuous data collection through the

387   SMART*health* platform, it was recognised early that prior district-level procurement of

388   essential CVD preventive medications, whilst affordable within typical procurement budgets,

389   would be inadequate to meet demand. While the short-term acquisition of additional

390   medication was supported by study funding (finally supporting ~50% of prescribed

391   medications), existing purchasing and supply chain processes that avoided stock-outs was

392   critical.

393

394   Second, workforce characteristics in rural Indonesia enabled implementation. A core element

395   of the theory of change was to generate community-level demand at the household level,

396   rather than relying on promoting healthcare seeking behaviour among largely asymptomatic

397   individuals. The presence of a community healthcare workforce already delivering care

398   through household visits provided task-sharing opportunities through workflow modification,

399   avoiding the need for an entirely new cadre of workers [23, 24].

400

401   Third, task-sharing was strongly facilitated by the ability of the district health agency to

402   authorize subsequent prescription of essential medications by nurses, with ongoing delegation

403   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

429 There are additional potential limitations to consider. The performance of the risk charts in

430 this population overall and in certain subgroups is uncertain, however this would not

431 introduce bias in the between-group comparisons. Self-report was used for medication use,

432 although the pre-specified secondary outcome of blood pressure provides some objective

433 verification. Another concern may be that the study was not powered to identify effects on

434 clinical events. However in the context of using drugs of proven efficacy and safety, blood

435 pressure would be considered an appropriate surrogate for CVD events [30]. Additionally, it

436 is possible that community members from intervention villages may have disclosed prior

437 exposure to the SMART*health* program to field researchers during follow-up, impacting on

438 blinded outcome assessment. We were unable to assess the extent to which this may have

439 occurred. A further potential limitation is that control villages were selected from sub-

440 districts served by the same primary healthcare center as the intervention villages, providing a

441 theoretical basis for contamination. In practice, very few patients currently seek and/or

442 receive CVD care at the primary healthcare center level. In addition, if there were any

443 contamination due to SMART*health*-exposed doctors treating control village community

444 members, this would bias the results towards the null. Finally, the small number and selected

445 nature of the villages included limits the generalizability of the findings.

446

447 While the results are encouraging, further research is important to facilitate and demonstrate

448 scalability and sustainability [31]. Relevant data will emerge from the economic and process

449 evaluations from this study; however, institutionalizing such interventions needs to address a

450 range of issues for effective health system integration. These include ensuring interoperability

451 with Indonesia's emerging eHealth strategy and infrastructure, drug and equipment supply

452 chains, workforce and management training, and alignment with existing healthcare

453 financing, social insurance and reimbursement mechanisms. Finally, it will be necessary to

454   broaden the disease focus to provide comprehensive primary healthcare services for a range

455   of common conditions for ultimate sustainability and maximum impact.

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605

606 *Figure legends*

607 Figure 1: Flowchart of participants through the study

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

609

610 *Online supplements*

611 **Supplement 1**

612 eAppendix1: SMART*health* program in Indonesia

613 eAppendix 2: Additional details on statistical methods

614 eFigure 1: SMART*health* logic model

615 eFigure 2: Study villages

616 eTable 1: Concordance between *kader*-identified and researcher-identified high-risk

617 individuals in the intervention villages

618 eTable 2: Baseline characteristics of the census population

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

620 up

621 eTable 4: Additional baseline characteristics of high-risk individuals

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

623 eFigure 3: Subgroup analyses for primary outcome

624 **Supplement 2**

625 Statistical Analysis Plan and deviations

626 **Supplement 3**

627 TIDieR Checklist

628