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Effects of a lifestyle intervention on cardiovascular risk among high-risk individuals for diabetes in a low- and middle-income setting: Secondary analysis of the Kerala Diabetes Prevention Program

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ABSTRACT

We aimed to examine whether a lifestyle intervention was effective in reducing cardiovascular disease (CVD) risk in individuals at high-risk of developing diabetes in a low- and middle-income setting. The Kerala Diabetes Prevention Program was evaluated by a cluster-randomized controlled trial (2013–2016) of 1007 individuals (aged 30–60 years) at high-risk for diabetes (Indian Diabetes Risk Score ≥ 60 and without diabetes) in Kerala state, India. Sixty polling areas in Kerala were randomized to intervention or control groups by an independent statistician using a computer-generated randomization sequence. Participants from 30 intervention communities received a 12-month structured peer-support lifestyle intervention program involving 15 group sessions and linked community activities, aimed at supporting and maintaining lifestyle change. The primary outcome for this analysis was the predicted 10-year CVD risk at two years, assessed using the Framingham Risk Score. The mean age at baseline was 46.0 (SD: 7.5) years, and 47.2% were women. Baseline 10-year CVD risk was similar between study groups. The follow-up rate at two years was 95.7%. The absolute risk reduction in predicted 10-year CVD risk between study groups was 0.69% (95% CI: 0.09% to 1.29%, $p = 0.024$) at one year and 0.69% (95% CI: 0.10% to 1.29%, $p = 0.023$) at two years. The favorable change in CVD risk with the intervention condition was mainly due to the reduction in tobacco use (change index: −0.25, 95% CI: −0.42 to −0.09). Our findings suggest that a community-based peer-support lifestyle intervention could reduce CVD risk in individuals at high-risk of developing diabetes in India.

Trial registration: Australia and New Zealand Clinical Trials Registry ACTRN12611000262909.

1. Introduction

Cardiovascular diseases (CVDs) are the leading cause of mortality globally, accounting for an estimated 17.9 million deaths in 2016, of which more than three quarters were in low- and middle-income countries (LMICs) (World Health Organization, 2017a). Individuals at high risk of developing type 2 diabetes are also at increased risk for developing CVDs (Gerstein et al., 2007; Levitan et al., 2004). Randomized controlled trials (RCTs) among high-risk individuals for type 2 diabetes have shown that structured lifestyle intervention programs focused on increasing physical activity, promoting healthy dietary habits and weight loss can improve CVD risk factors in addition to

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reducing diabetes incidence (Baker et al., 2011; Sun et al., 2017). Secondary analysis of some of these RCTs conducted in high-income countries has found that lifestyle interventions reduce absolute 5-year CVD risk by 1.08% (Dunbar et al., 2015) and 10-year CVD risk by 0.48–2.23% (Davies et al., 2016; Lipscomb et al., 2009). However, similar studies are not available from LMICs, where the burden of CVDs is high and increasing (World Health Organization, 2017a).

CVD risk prediction uses a combined measure based on several risk factors to determine the absolute risk of developing a CVD event in a given period of time (Damen et al., 2016). Several CVD guidelines recommend risk prediction as a means to identify high-risk groups who could be targeted by prevention strategies (Pearson et al., 2002; Robson, 2008; World Health Organization, 2017b). Many risk prediction models have been developed to predict an individual's risk for developing a CVD event over the next 5 or 10 years, with the Framingham Risk Score (D'Agostino et al., 2008) being the most widely used risk score globally (Damen et al., 2016). Studies from different populations have now shown that the Framingham Risk Score performs better than other CVD risk scores in identifying those at high risk of developing CVD events, including India (Garg et al., 2017; Gaziano et al., 2016).

We conducted a cluster-RCT to evaluate the effects of a community-based, structured peer-support lifestyle intervention program - Kerala Diabetes Prevention Program (K-DPP) - among individuals at high-risk for type 2 diabetes in India. The primary and secondary outcome results of the K-DPP trial have been published elsewhere (Thankappan et al., 2018). In addition to a non-significant 12% relative risk reduction in diabetes incidence at two years, the K-DPP intervention resulted in significant improvements in certain other key CVD risk factors (Thankappan et al., 2018). However, it not known whether these changes have translated into reduced CVD risk in this high-risk population, which may be more impactful from a clinical and public health point of view. Therefore, we conducted a secondary analysis of the K-DPP trial data to examine whether the intervention was effective in reducing the predicted 10-year CVD risk, assessed using the Framingham Risk Score.

2. Methods

2.1. Study design and participants

The details of the K-DPP study design including participant recruitment and screening have been previously reported (Sathish et al., 2019a; Sathish et al., 2019b; Sathish et al., 2013), and the study protocol is available from https://www.ncbi.nlm.nih.gov/pubmed/24180316. Briefly, the randomized evaluation of K-DPP was undertaken in 60 randomly-selected polling areas (electoral divisions) from Neyyattinkara taluk (sub-district) in Trivandrum district of Kerala state in India. Fig. 1 shows the K-DPP CONSORT flowchart. These polling areas were randomly assigned (1:1) to a control group or a lifestyle intervention group by an independent person with a randomization sequence generated by a computer program. Individuals aged 30–60 years were identified from the electoral roll of the selected polling areas and were approached at their households by trained field staff. A total of 3421 potential participants were screened for eligibility and those with a history of type 2 diabetes or other major chronic illnesses, taking medications affecting glucose tolerance (e.g., corticosteroids), or who were illiterate in the local language were excluded. We also excluded pregnant women. Those satisfying the eligibility criteria (n = 2586) underwent a two-step screening procedure involving a diabetes risk score and a 2-h 75-g oral glucose tolerance test (OGTT) (Sathish et al., 2019b). The Indian Diabetes Risk Score (IDRS), which is comprised of age, family history of type 2 diabetes, physical activity and waist circumference (Mohan et al., 2005), was administered by trained staff, and those with an IDRS score ≥60 (n = 1529) were invited to attend clinics organized in local neighborhoods to undergo an OGTT. Of 1209 participants who attended the clinics, those with type 2 diabetes on the OGTT were excluded (n = 202) and referred to healthcare facilities for treatment and care. Type 2 diabetes was diagnosed according to the American Diabetes Association criteria (fasting plasma glucose ≥126 mg/dl and/or 2-h plasma glucose ≥200 mg/dl) (American Diabetes Association, 2018). The remaining 1007 individuals were recruited to the trial (control group: 507; intervention group: 500).

2.2. Intervention

The details of the intervention program, including its development, theoretical background, cultural adaptation, and implementation fidelity have been reported previously (Daivadanam et al., 2013; Mathews et al., 2017; Sathish et al., 2013; Thankappan et al., 2018). Briefly, the intervention was designed based on a needs assessment study (Daivadanam et al., 2013) along with cultural adaptation from the Finnish Good Ageing in Lahti Region Program (Absetz et al., 2007), the Australian Greater Green Triangle Diabetes Prevention Project (Laatikainen et al., 2007) and the US Diabetes Prevention Program (Diabetes Prevention Program Research Group, 2002). The core functions of peer support identified in the US Peers for Progress program (Boothroyd and Fisher, 2010) further informed the intervention development. The intervention consisted of 15 group sessions delivered over a period of 12 months. All sessions were conducted in local neighborhoods in community buildings (e.g., schools, community halls) during weekends at times that were convenient for participants. The K-DPP staff members delivered an introductory session (60–90 min) to introduce the participants to the program and its mentoring style. Experts in the field of diabetes, nutrition, and physical activity delivered two half-day sessions focusing on prevention and management strategies for diabetes. Trained peer leaders (one male and one female per group), who were identified from within the group, delivered monthly group sessions (60–90 min per session). The objectives of the lifestyle intervention were to increase physical activity, promote healthy eating habits, quit tobacco use, reduce alcohol consumption, maintain ideal body weight, and ensure adequate sleep. Additionally, participants were encouraged by their peer leaders to engage in community activities such as kitchen gardening, yoga training, and walking groups in order to support the maintenance of lifestyle change and involvement of other family members and residents from their community. Control group participants received standard advice about lifestyle change through a health education booklet at baseline.

2.3. Measurements

Participants were assessed at baseline, one year, and two year. During each assessment, data on socio-demographic characteristics, lifestyle behaviors, and medical history were collected using standardized questionnaires by trained staff. They also measured anthropometry (height, weight, waist and hip circumferences, and body composition) using standard protocols (Sathish et al., 2013). Blood pressure (BP) was recorded three times using the Omron automatic blood pressure monitor (model IA2) with an interval of at least 3 min between the readings. The average of the second and third BP readings was considered as the BP of participants. Blood samples were collected for OGTT, HbA1c, and lipids, according to standard protocols.(Sathish et al., 2013) The blood samples were centrifuged within 30min of collection and were transported to a nationally accredited laboratory in boxes containing dry ice. Hexokinase method was used to measure plasma glucose on a COBAS 6000 analyzer. High-performance liquid chromatography method was used to measure HbA1c on a D-10 BIORAD analyzer. Enzymatic methods were used to measure lipids on a COBAS 6000 analyzer. The kits for measuring plasma glucose, lipids and HbA1c were supplied from Roche Diagnostics, Switzerland. LDL cholesterol was estimated using the Friedewald equation (Friedewald

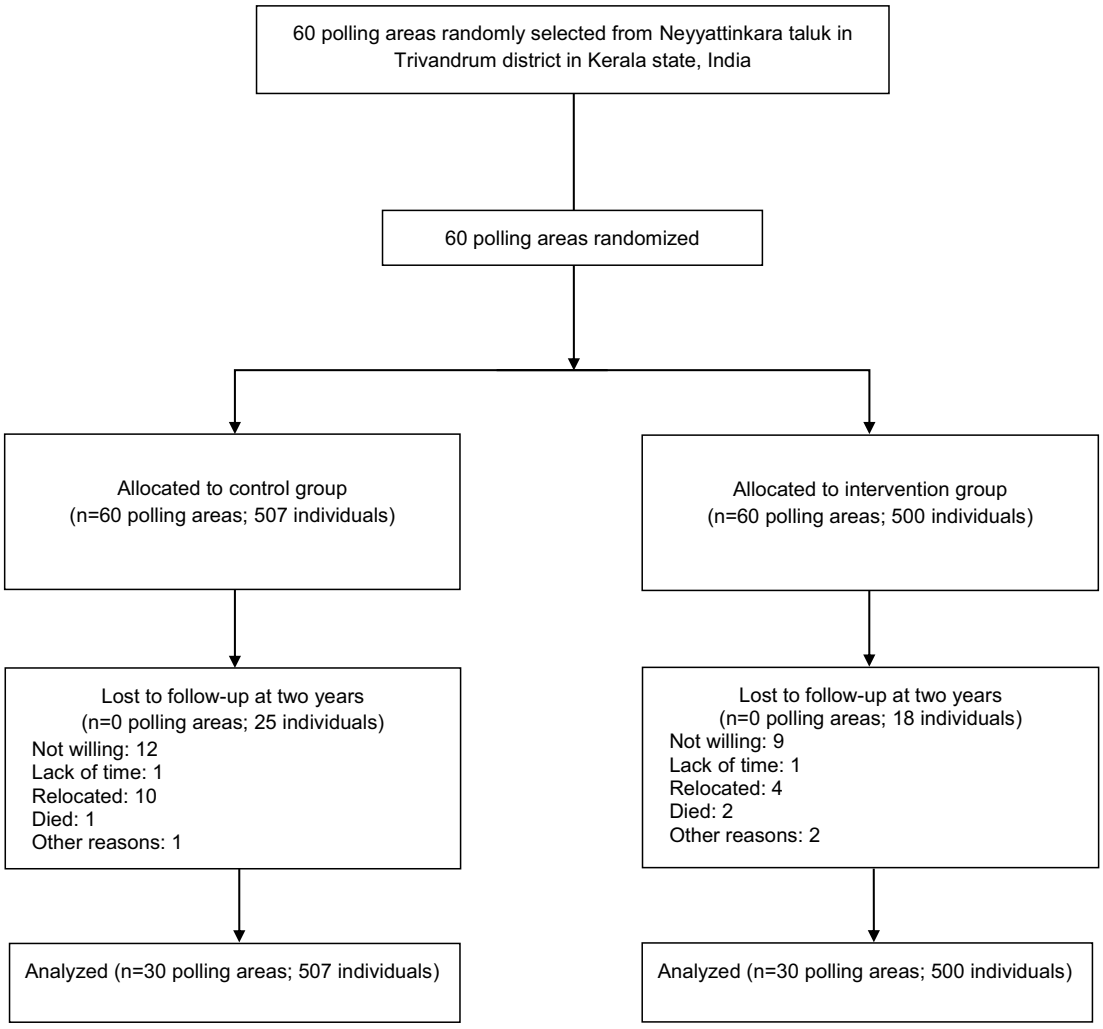

Fig. 1. K-DPP CONSORT flowchart.

et al., 1972) for those with triglycerides ≤400 mg/dl and for the rest, values from the direct method were used.

2.4. Outcomes

The primary outcome for this analysis was predicted 10-year CVD risk based on the two-year evaluation, using the Framingham Risk Score (D'Agostino et al., 2008). We estimated the 10-year CVD risk using the original equation of the Framingham Risk Score (Supplementary file) for each participant at baseline and follow-up examinations. The equation includes age, sex, current smoking, systolic BP, type 2 diabetes, total cholesterol, treatment for hypertension, and HDL cholesterol (D'Agostino et al., 2008). Instead of current smoking, we used current tobacco use (smoking or smokeless tobacco), since no women in our study smoked, while 2.3% were using smokeless tobacco. Current tobacco use and treatment for hypertension were ascertained by the following questions: "Did you use any tobacco products (cigarettes, bidis, cigars, hookah, chewing tobacco or snuff) in the last 30 days" and "Are you currently taking medications for high blood pressure or hypertension?", respectively. Since participants were free of diabetes at baseline, they had zero points for the diabetes component of the risk score at baseline. Secondary outcomes included modifiable risk factors included in the Framingham Risk Score namely, current tobacco use, systolic BP, diabetes, total cholesterol, treatment for hypertension, and HDL cholesterol.

2.5. Statistical analysis

Mean (standard deviation, SD) for continuous variables and frequency (%) for categorical variables were used to summarize the data. Mixed-effects linear regression models based on maximum likelihood estimation were used to examine the difference in mean change in the predicted 10-year CVD risk between study groups at one and two years. We assigned fixed effects for the study group (intervention vs. control), timepoint (follow-up vs. baseline), and study group-by-timepoint interaction. Random effects were specified for clusters and participants. The statistical significance in mean change between study groups was assessed by *p*-value for the study group-by-timepoint interaction.

To examine the effects of the intervention on modifiable risk factors included in the Framingham Risk Score, we used mixed-effects linear regression models for continuous variables and log-binomial models estimated using generalized estimating equations (GEE) with an exchangeable working correlation structure and robust standard errors (to account for clustering by polling areas) for categorical variables. The results of GEE models are presented as relative risk (RR) along with 95% confidence interval (CI) and *p*-value.

We quantified the contribution of change in each risk factor, included in the Framingham Risk Score, to the intervention effect on the predicted 10-year CVD risk. For this, we multiplied the magnitude of change (or a transformation if indicated in the Framingham Risk Score) with the corresponding coefficient in the Framingham Risk Score equation (D'Agostino et al., 2008). This analysis was performed to

identify risk factors that could be better targeted for intervention.

As a sensitivity analysis, the missing values for components necessary to calculate the Framingham Risk Score (11% at one year and 9% at two year) were imputed using multiple imputation (MI), accounting for clustering by polling areas (Goldstein et al., 2009). MI was performed using chained equations with 20 imputations, and mixed-effects models were run on each of the 20 imputed datasets and the results were combined using Rubin's rule (Little and Rubin, 1987). A two-sided $p < 0.05$ was considered to be statistically significant. All analyses were performed by Stata 14.2 version (StataCorp LP, College Station, Texas, USA).

2.6. Ethics approval

The study protocol was approved by ethics committees of the Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum in India (SCT/IEC-333/May 2011) and Monash University (CF11/0457-2011000194) and the University of Melbourne in Australia (1441736). The study also received approval from the Health Ministry Screening Committee of the Government of India. Written informed consent was obtained from all the participants. The trial was registered in the Australia and New Zealand Clinical Trials Registry (ACTRN12611000262909).

3. Results

The study participants were recruited in 2013 and followed-up until early 2016. The mean age of participants at baseline was 46.0 years (SD: 7.5), and 47.2% were women. Baseline characteristics of clusters and participants were similar in the two study groups (see Appendix A). The prevalence of certain key CVD risk factors was high at baseline, as reported previously (Sathish et al., 2017b). For example, one-third of men (34%) were current tobacco users, 98% had no leisure-time exercise, 79% were not consuming fruit and vegetables daily, 69% were overweight or obese, 22% were hypertensive, and 85% had abnormal lipids. All clusters and 95.7% of participants were followed up after a median of 24 months (95.1% in the control group; 96.4% in the intervention group).

The predicted 10-year CVD risk was similar between study groups at baseline (see Appendix A). At one and two years, the CVD risk increased in the control group by 1.14% and 2.30% from baseline, respectively. While in the intervention group, the respective increase was lower at 0.45% and 1.60%. The between-group difference was −0.69% (95% CI: −1.29% to −0.09%) at one year and by −0.69% (95% CI: −1.29% to −0.10%) at two years (see Table 1). These results were similar to those from MI analysis (between-group difference: −0.73% [95% CI: −1.37% to -0.09%] at one year; −0.73% [95% CI: −1.35% to −0.10%] at two years). The significant reduction in CVD risk with the intervention condition was mainly due to the reduction in tobacco use, with lesser impacts from the reduction in diabetes incidence and improvements in HDL-cholesterol and systolic BP (Fig. 2).

Table 2 shows the changes in modifiable risk factors included in the Framingham Risk Score by study group and timepoints. At two years, compared with the control participants, those in the intervention group were less likely to use tobacco by 21% (RR: 0.79, 95% CI: 0.60 to 1.05), to have diabetes by 12% (RR: 0.88, 95% CI: 0.66 to 1.16), and to be taking anti-hypertensive medications by 4% (RR: 0.96, 95% CI: 0.66 to 1.40), and more likely to have a lower total cholesterol by 0.52 mg/dl. However, these differences were not statistically significant (all $p > 0.05$). While the mean HDL cholesterol decreased in both study groups, the decrease was significantly smaller in the intervention group (mean difference between study groups: 1.48 mg/dl, $p = 0.027$) at two years.

4. Discussion

To our knowledge, this is the first study from an LMIC setting to examine the effects of a lifestyle intervention program on the predicted 10-year CVD risk in individuals at high-risk for type 2 diabetes. We found that the predicted 10-year CVD risk (assessed by the Framingham Risk Score) reduced significantly by 0.69% in the intervention group, compared with the control group, at two years. This favorable change in CVD risk with the intervention condition was mainly due to the reduction in tobacco use.

Secondary analysis of a few lifestyle-related RCTs on high-risk individuals for diabetes from high-income countries has examined the intervention effects on CVD risk. In the DEPLOY study from the United States, the absolute 10-year CVD risk predicted using the UKPDS engine reduced by 2.23% (95% CI: 0.14% to 4.33%) in the intervention group, compared with the control group, at 12 months (Lipscomb et al., 2009). In the Let's Prevent Diabetes cluster-RCT from the UK, the absolute risk reduction of 10-year CVD risk was 0.48% (95% CI: −0.37% to 1.34%) between study groups at 36 months (Davies et al., 2016). In the Melbourne Diabetes Prevention Study, the absolute 5-year CVD risk decreased by 1.08% ($p = 0.013$) in the intervention group compared with the control group at 12 months (Dunbar et al., 2015). The resource-intensive nature of these lifestyle intervention programs from high-income countries often limits the scalability of such initiatives in LMIC settings such as India. On the other hand, K-DPP is a low-cost (US$22.5 per participant) (Thankappan et al., 2018) and contextually relevant lifestyle intervention, which had very good reach and adoption in the community (Aziz et al., 2018). There was also broader diffusion to other family and community members who were not formally involved in the program (Aziz et al., 2018). These findings indicate the feasibility and the potential for scalability of this intervention on a large-scale in India. The actual reduction in CVD risk would be greater than what has been observed in this analysis, as the intervention resulted in significant changes in certain other key CVD risk factors (not included in the Framingham Risk Score) such as alcohol use, fruit and vegetable intake, and IDRS score at two years (Thankappan et al., 2018). Furthermore, a substantial proportion of intervention participants increased their physical activity levels and improved their diet compared to those in the control group (Aziz et al., 2018).

There was a significant improvement in HDL-cholesterol and non-significant reductions in mean systolic BP and total cholesterol, the incidence of diabetes, and the prevalence of tobacco use and treatment of hypertension with the intervention at two years. The collective effects of changes in these risk factors resulted in a significant reduction in the predicted 10-year CVD risk in the intervention group, compared to the control group. Multiplying the magnitude of change in each risk

Table 1
Changes in predicted 10-year CVD risk (%) based on the Framingham Risk Score by study group.

	Mean change (SE) from baseline to one year	Difference (95% CI)	P	Mean change (SE) from baseline to two years	Difference (95% CI)	P
Control group	1.14 (0.21)	−0.69 (−1.29 to −0.09)	0.024	2.30 (0.21)	−0.69 (−1.29 to −0.10)	0.023
Intervention group	0.45 (0.22)			1.60 (0.22)		

SE, standard error; CI, confidence interval. Mixed effects linear regression was used to estimate the mean change (SE) within study groups and the difference in mean change (and 95% CI) between study groups.

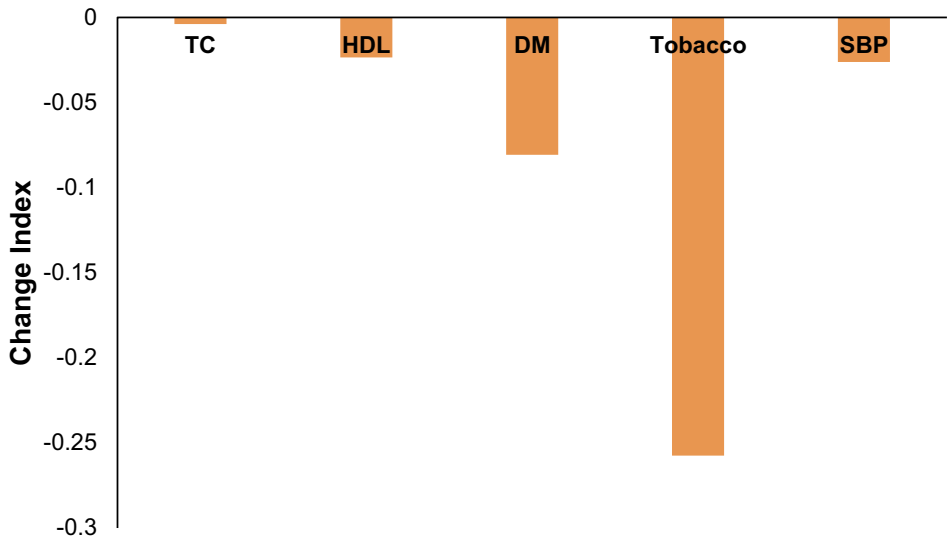

Fig. 2. TC, total cholesterol (in mg/dl); HDL, high density lipoprotein (in mg/dl); DM, diabetes mellitus; SBP, systolic blood pressure (in mmHg). Change index was estimated by multiplying the magnitude of change in each risk factor (or a transformation if indicated in the Framingham Risk Score) with its corresponding coefficient in the Framingham Risk Score equation.

factor to its coefficient in the Framingham risk equation showed that the favorable change in CVD risk with the intervention was mainly due to the reduction in tobacco use. This suggests that lifestyle intervention strategies aimed at reducing diabetes incidence in high-risk individuals should also focus on tobacco use cessation, in addition to promoting other lifestyle changes, to achieve CVD risk reduction.

Our study has several strengths. The K-DPP trial was conducted in the Indian state of Kerala, which has a very high burden of key CVD risk factors (Sathish et al., 2012; Sathish et al., 2017a). The epidemiological transition that is currently occurring in Kerala is indicative of what will happen in other states in India in the coming years as well as in many other LMICs (India State-Level Disease Burden Initiative Collaborators, 2017). Therefore, the identification of appropriate CVD risk reduction strategies in this setting will enable proactive policymaking in other states of India as well as other LMICs that will undergo a similar transition in the future. Other strengths include a very high follow-up at two years (95.7%), high rates of data completeness and a good representation of women (nearly half of the participants were women) unlike other trials from India (Ramachandran et al., 2006; Weber et al., 2016). However, there are also some limitations. The analyses for this paper are post hoc, and thus the results should be considered as hypothesis-generating. The follow-up was relatively short, which did not allow us to examine cardiovascular outcomes. Our study participants were identified on the basis of a risk score, and an OGTT was performed

Table 2
Changes in modifiable risk factors included in the Framingham Risk Score at one and two years by study group.

	Control group	Intervention group	Difference (95% CI)[a]	P
	Mean change from baseline (SE)			
Total cholesterol (mg/dl)				
One year	−6.64 (1.35)	−5.10 (1.38)	1.54 (−2.24 to 5.32)	0.43
Two year	−4.59 (1.36)	−5.10 (1.36)	−0.52 (−4.29 to 3.26)	0.79
HDL-cholesterol (mg/dl)				
One year	−2.92 (0.47)	−1.35 (0.48)	1.57 (0.25 to 2.89)	0.020
Two year	−3.57 (0.47)	−2.09 (0.48)	1.48 (0.17 to 2.80)	0.027
Systolic blood pressure (mmHg)				
One year	−1.08 (0.56)	−1.11 (0.57)	−0.03 (−1.59 to 1.53)	0.97
Two year	0.28 (0.57)	−0.92 (0.57)	−1.22 (−2.80 to 0.35)	0.13
	Control group	Intervention group	Relative risk (95% CI)[b]	P
	n/N (%)	n/N (%)		
Diabetes[c]				
One year	46/462 (10.0)	42/440 (9.5)	0.96 (0.64 to 1.43)	0.84
Two year	79/463 (17.1)	68/456 (14.9)	0.88 (0.66 to 1.16)	0.36
Tobacco use[d]				
One year	82/495 (16.6)	73/487 (15.0)	0.80 (0.64 to 0.98)	0.035
Two year	80/482 (16.6)	72/482 (14.9)	0.79 (0.60 to 1.05)	0.11
Treatment for hypertension				
One year	49/495 (9.9)	42/487 (8.6)	0.98 (0.70 to 1.38)	0.90
Two year	48/482 (10.0)	41/482 (8.5)	0.96 (0.66 to 1.40)	0.84

SE, standard error; CI, confidence interval; HDL, high density lipoprotein.
[a] Difference in mean change between study groups was estimated using mixed-effects linear regression.
[b] Generalized estimating equation was used to estimate the relative risk for categorical variables.
[c] Diabetes was defined as fasting plasma glucose ≥126 mg/dl and/or 2-h plasma glucose ≥200 mg/dl and/or clinically diagnosed by a physician and taking glucose-lowering medications.
[d] Smoked cigarettes, bidis, cigars or hookah, or used chewing tobacco or snuff in the last 30 days.

only to exclude people with diabetes. Thus, it is the case that a large proportion of individuals had either normal glucose or isolated impaired fasting glucose (Sathish et al., 2017b), which might have reduced the intervention effects on measured CVD risk. Although the Framingham Risk Score is the most widely used risk score globally, it has not yet been validated for CVD risk prediction among high-risk individuals for type 2 diabetes. However, any possible underestimation or overestimation of risk should happen similarly in both study groups, and thus, it should not affect comparisons.

5. Conclusion

In conclusion, our study findings suggest that this low-cost, community-based peer-support lifestyle intervention could significantly reduce CVD risk among individuals at high-risk of developing type 2 diabetes in India. Tobacco use cessation should be considered as one of the lifestyle change objectives in diabetes prevention programs to achieve CVD risk reduction. While the likely clinical benefits of this intervention in terms of CVD risk reduction are probably only marginal, the public health impact of the absolute reduction of 0.69 percentage point in our study is equivalent to preventing 690 people from increasing their CVD risk, if the program were taken to scale in a population of 100,000 individuals at high risk of type 2 diabetes. As we learn more about how to deliver such community-based interventions to reduce CVD risk more effectively and efficiently in large populations, it is likely that the public health impact can be further increased (Ranjana et al., 2020). More importantly, a longer-term follow-up of these participants is necessary to examine whether a reduction in CVD outcomes could be achieved with this intervention.

CRediT authorship contribution statement

Mojtaba Lotfaliany: Conceptualization, Data curation, Formal analysis, Methodology, Software, Validation, Visualization, Writing - original draft, Writing - review & editing.**Thirunavukkarasu Sathish**: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing.**Jonathan Shaw**: Conceptualization, Funding acquisition, Methodology, Writing - review & editing.**Emma Thomas**: Writing - original draft, Writing - review & editing.**Robyn Jennifer Tapp**: Conceptualization, Funding acquisition, Methodology, Writing - review & editing.**Nitin Kapoor**: Methodology, Writing - review & editing.**Kavumpurathu Raman Thankappan**: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing - review & editing.**Brian Oldenburg**: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing - review & editing.

Declaration of competing interest

The authors declare that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ypmed.2020.106068.

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