Title: Worksite Lifestyle Program for Reducing Diabetes and Cardiovascular Risk in India
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Abstract

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Asian Indians have high rates of diabetes, prediabetes and cardiometabolic risk factors. There is strong evidence that lifestyle change, particularly weight loss, increasing physical activity, and improving diet quality can prevent or delay diabetes, reduce cardiometabolic risk factors such as elevated glucose, plasma lipids, and blood pressure, and improve outcomes among individuals with diabetes. Implementing lifestyle change education and support at the worksite may be an effective and cost-effective method to deliver prevention in a way that is acceptable, accessible, and sustainable and overcomes barriers to lifestyle change (e.g., lack of time or resources). Building off previous work by the international study team, this study proposes implementing and evaluating in a pre-post design trial the acceptability, delivery, effectiveness, and cost-effectiveness of a worksite-based lifestyle improvement package including a peer-led lifestyle change education program augmented with changes in the worksite environment that promote social support, healthy eating and exercise. The lifestyle education program will include 2000 adults with prediabetes (HbA_{1c} of 5.7-6.4%) or unmedicated diabetes ($HbA_{1c} \geq 6.5\%$ identified at screening) across eight diverse worksites in India (changes to the worksite environment will impact a much broader population of employees). A mixed methods approach will be used to evaluate implementation of the program. The study aims to measure: (1) Success of implementation in terms of program adoption (participation and changes in weight and diet and physical activity behaviors among lifestyle class participants); fidelity to the program (activities of study-affiliated worksite staff; changes to the food options at the worksite canteen; management support for the program; and changes in the worksite environment); and program acceptability as reported by employees, managers, supervisors, and lifestyle education program participants and dropouts during in-depth, semi-structured interviews and focus group discussions. (2) Program effectiveness by evaluating the number of cardiometabolic risk goals reached for reductions in blood pressure, triglycerides, and HbA_{1c} (the primary outcome) and through changes in secondary outcomes including rates of diabetes incidence and regression to normoglycemia and changes in anthropometry, lipids, and fasting glucose. (3) Value and return on the investment of the program for employers by assessing program costs, cost-effectiveness, and changes in staff productivity, absenteeism, health status, and quality of life. This project will deliver scientific innovations (lifestyle education programs with text message supports during maintenance) with social innovations (educated peer health educators delivering a program to a large at risk population) and business innovation (worksite stakeholder commitment and partnering researchers to help deliver the program with fidelity, improve the workplace health environment, and evaluate the model). If the program is shown to be feasible, acceptable, effective, and cost-effective at these worksites, the program could be disseminated to other worksites throughout India and elsewhere.

Narrative

This study will test the implementation, effectiveness, cost-effectiveness, and acceptability of a worksite lifestyle improvement program that includes lifestyle education classes led by trained individuals from the worksite and improvements in the worksite environment that will make it easier for employees to lose weight, exercise more, and eat a healthier diet. If this program is shown to be successful, it can be implemented at worksites across India and beyond.

Specific Aims

Diabetes has reached epidemic proportions globally; some countries, like India, are acutely affected. At least 65.1 million people in India have diabetes and a further 77.2 million have prediabetes, many of whom are working age adults.[1,2] Diabetes has profound implications for health systems (personnel and resources to provide care), individual and family finances (high costs of care particularly where insurance does not exist, loss of wages due to lost work time), individuals (debilitating secondary complications, lower quality of life, shorter life expectancy), and worksites (lower productivity, greater lost work time).[1,3-5]

Data from randomized controlled trials unequivocally show that lifestyle modification reduces diabetes incidence in people with prediabetes, improves glycemic control and cardiovascular risk profiles, and has beneficial effects on diabetes complications;[6-17] however, community-based implementation of these programs is challenging because they are costly and require large commitments of staff and participant time.[18] Translation to the broader population will require creative solutions to lower financial and personnel costs, and these programs need to be delivered in a way that is acceptable and accessible, cost-effective for payers, culturally appropriate, and easy to disseminate and maintain. Delivering lifestyle programs at worksites, using the existing structure of worksite health facilities for testing and training and utilizing trained worksite staff as peer health educators, could be an effective and cost-effective approach for delivering lifestyle education, may overcome many individual-level barriers to participation in a lifestyle education program (e.g., lack of time and social support, inability to locate resources), and could be beneficial to employers (e.g., higher employee satisfaction, retention, and possibly less lost productivity due to illness).[19-24]

Members of the research team proposing this work have developed and tested a successful model of lifestyle education for use in India (D-CLIP, Diabetes Community Lifestyle Improvement Program[25]) and have conducted many studies in India and elsewhere which have shown positive health effects of improving diet quality.[26-40] Building on this research, we propose implementing and evaluating the acceptability, delivery, effectiveness, and cost-effectiveness of a worksite-based lifestyle improvement package: a peer-led lifestyle change program with group-based classes on weight loss/maintenance, dietary improvements and increasing physical activity delivered in worksite environments that facilitate these changes (for example, by offering healthy food options in the canteen). Since the evidence unequivocally shows that lifestyle change is efficacious and essential for diabetes prevention and management and is already part of authoritative guidelines[41] and given that this is an implementation trial that could result in the subsequent scale-up of efforts, we propose using a pre-post trial design to assess if the intervention package can prevent diabetes and cardiovascular disease risk factors in adults with prediabetes (HbA_{1c} of 5.7-6.4%) or unmedicated diabetes ($HbA_{1c} \geq 6.5\%$, but currently not taking diabetes medications) in India. Among 2000 people with prediabetes or early diabetes identified from eight diverse worksites in India with stakeholder commitment, we will use a mixed methods approach to evaluate a worksite-based, culturally tailored intervention package. The study aims:

Aim 1: To measure the success of implementation and inform the scalability of this intervention program by evaluating: (a) *program adoption* by assessing participation and changes in weight and diet and physical activity behaviors among lifestyle class participants; (b) *fidelity to the program* by assessing activities of study-affiliated worksite staff; changes to the food options at the worksite canteen; management support for the program; and changes in the worksite environment; and (c) *acceptability of the program* through (i) in-depth, semi-structured interviews with study site management and employees and lifestyle education program dropouts and (ii) focus group discussions with lifestyle education program participants.

Aim 2: To measure the effectiveness of the program among participants by evaluating the change in number of individuals reaching two or more of cardiometabolic risk goals, namely reductions in blood pressure, triglycerides, and HbA_{1c} (the primary outcome), and through changes in secondary outcomes including rates of diabetes incidence and regression to normoglycemia and changes in anthropometry, lipids, and fasting glucose.

Aim 3: To measure the value and return on investment of the intervention for employers by assessing program cost and cost-effectiveness and changes in staff productivity, absenteeism, health status, and quality of life.

If the program is shown to be feasible, acceptable, effective, and cost-effective at these worksites, the results of this study will be used to make recommendations and dissemination plans on how to implement and sustain lifestyle interventions at worksites to improve the health of workers and communities for other sites within these companies, other Indian worksites, organizations involved in promoting worksite wellness and/or chronic disease prevention, and to India's National Programme for Prevention and Control of Diabetes, Cardiovascular Diseases, and Stroke. Furthermore, lessons from this study can be used to make recommendations or plan studies of similar worksite programs in the U.S. and other settings outside of India.

Significance

The Diabetes Epidemic: Type 2 diabetes mellitus (T2DM) is an economically costly disease and a major cause of morbidity and mortality globally.[4,42] Eighty percent of the 382 million people worldwide with diabetes live in low- and middle-income countries.[1] Asian Indians living worldwide are particularly susceptible to developing T2DM, with high prevalences of T2DM and T2DM risk factors (e.g., beta-cell dysfunction, central adiposity), higher rates of progression from prediabetes to diabetes,[43] and lifestyles that pre-dispose to T2DM (e.g., high-fat, low fiber diets and low physical activity).[2,44-46] Asian Indians fare worse than several other populations after developing T2DM (poor glycemic control, higher rates of complications).[47-50]

Lifestyle and Diabetes and Cardiovascular Disease (CVD) Risk Factors: Lifestyle intervention participants in the multi-center, U.S. Diabetes Prevention Program (DPP) had a 58% reduction in diabetes incidence compared to controls, with results consistent across race-ethnicity, sex, and age.[14] In the DPP and other similar studies, lifestyle change was shown to have lasting effects, with significant improvements subsisting 3-14 years after the intervention.[9,11,12,51] The Look AHEAD study, which assessed the effectiveness of a lifestyle intervention program for preventing CVD endpoints in individuals with diabetes, showed that intervention participants did significantly better than controls in terms of weight loss and reductions in CVD risk factors, required less medications to manage blood pressure and lipid levels, and had a greater remission to normoglycemia than controls.[17,52,53] Lifestyle interventions have beneficial effects on other cardiometabolic risk factors, including low physical activity, poorly controlled blood pressure and plasma lipids, and on incidence of retinopathy, chronic kidney disease, urinary incontinence, and disability.[8,13-16]

Improving diet quality is an important component of lifestyle interventions, particularly given the negative health impacts of shifting from diets high in fresh produce and whole grains to diets high in refined carbohydrates and added sugars.[28,30] High quality diets (e.g., low in trans fats and glycemic load and high in fiber) decrease the risk for diabetes[38,54-57] and are important for maintaining glucose control and reducing CVD risk among individuals with diabetes.[58,59] Simply substituting brown rice for white rice as a staple food item significantly reduces fasting glucose and insulin levels.[40] Lack of awareness of health benefits, texture, palatability, scarcity, and cost are barriers to consumption of whole grains but promoting health benefits and subsidies to reduce cost are strategies that might increase consumption.[27,31,34,60,61]

Diabetes Prevention at the Worksite: People with diabetes have twice the rate of premature retirement than the rest of the population and compared to their peers without diabetes, are more likely to be unemployed, take more sick days, and report more work limitations.[62,63] These factors affect the overall productivity of worksites and lead to losses in profits for companies;[62] therefore, preventing diabetes and diabetes-related complications can be economically advantageous for companies.[24]

Worksite-based interventions can overcome barriers to healthy lifestyle choices by providing resources at a place and time where individuals spend much of their week and a socially supportive environment for change. Worksite-based health promotion programs have shown positive impacts on employees and worksites; a meta-analysis[19] of worksite-based physical activity programs reported that participants showed significant positive improvements in cardiometabolic risk factors (e.g., fitness, adiposity, and fasting glucose) and lower absenteeism and job stress and a worksite-based education program to improve employee diets resulted in significant improvements in diet quality.[20,64] Worksite wellness programs and intervention programs targeting diabetes prevention and weight loss have also shown positive effects on both mental (increased feelings of calmness, happiness, and ability to cope with stress) and physical (improvements in diet and physical activity behaviors, aerobic fitness, anthropometry, blood pressure, lipid profiles, plasma glucose) health.[21-23] The effects of these studies can be lasting, with one trial noting that risk factor improvements still persisted two years after intervention delivery.[22,23] In another study, even though health-related impact decreased over the seven years of follow-up, employee retention remained better among intervention participants.[65]

Worksite-based programs must address both individual health behaviors and the work environment.[66,67] In a recent review, screenings and health assessments, environmental changes to support the intervention (e.g., low-cost healthy food choices, places for physical activity), and group-based health education classes were specified as components of successful worksite interventions.[24] Management support has been shown to be highly influential in terms of the effectiveness of health programs in a number of settings,[68] and worksites with a staff person dedicated to delivering health education were 10.3 times more likely than other worksites to have comprehensive health promotion programs.[66]

Delivering lifestyle education in workplaces with a focus on improving the worksite environment,

collaborating with management, and training peers as health educators would be an innovative way to scale and translate diabetes and CVD prevention efforts. This research team has considerable experience in translational research and lifestyle education and change in India.[25,27,28,32,33,37,40,69] Building on this experience, we propose conducting a pre-post implementation trial to assess the acceptability, feasibility, and impact of a worksite-based lifestyle education program taught by trained peer educators and supplemented with changes in the worksite environment (e.g., offering healthy options in the work canteen, creating a supportive climate for lifestyle class participation) for employees with prediabetes and diabetes at eight worksites in India. This project will use a mixed methods approach to assess the intervention and its implementation, enabling well-supported recommendations for sustaining and implementing this intervention.

Innovation

We propose to implement and test a worksite-based lifestyle education program focusing on weight loss, dietary improvement, and increasing physical activity to individuals at risk of diabetes and/or CVD at eight diverse worksites in India (see Letters of Support). Integrated innovation theory posits that in order for an intervention to be successful in complex situations (e.g., the community), it must integrate scientific/technological, social, and business innovations.[70] This project fulfills this requirement: It delivers scientific innovations (lifestyle education programs with text message supports during maintenance) with social innovations (trained peer health educators delivering a program to a large at risk population) and business innovation (worksite stakeholder commitment and partnering researchers to help deliver the program with fidelity, improve the workplace health environment, and evaluate the model). The packaging of lifestyle education with environmental changes at the worksite level, implemented through an academic-industry partnership, is rarely done, particularly in India, a population with acutely high risk for diabetes and diabetes-related complications, and if successful could provide a model for innovative delivery of lifestyle education.

The lifestyle curriculum will be based on the program developed for the D-CLIP study,[25] a randomized translational trial of lifestyle modification delivered to community members at a diabetes care clinic in India. Recommendations for dietary quality improvements will also build on research conducted by members of the study team.[26-40] Applying this knowledge at the worksite represents the movement from clinic-based translational work to the broader community and allows the scaling of the intervention program from a single site, focused population to multiple locations and broader populations. Furthermore, delivering a diabetes prevention program at worksites in India at no cost to the employee can overcome many of the barriers to lifestyle change (e.g., cost of classes, lack of time, inability to locate acceptable resources for weight loss) and worksite support of the program might be a source of motivation for participants.

The intervention will include a broader range of individuals [selected by glycated hemoglobin (HbA_{1c}) testing] who could benefit from lifestyle change than have been included in previous translational research studies, namely both individuals with prediabetes and those with unmedicated diabetes. This population represents the larger community of individuals at risk of developing diabetes-related outcomes and complications.

This innovative worksite-based program leverages existing worksite resources (space, health facilities, employees) to deliver the intervention package, which includes lifestyle intervention classes and broader changes in the worksite environment. Peer educators, identified from the worksite and trained by professional health educators to deliver the program, can assist in sustaining the program, offer practical suggestions for program improvement and overcoming participant barriers, and act as examples for their peers. Classes will be dynamic and group-based, including scripted lessons on health topics (to maintain fidelity to the message across sites) followed by group-based activities and discussions that can be tailored to the individual needs of each lifestyle class and worksite. The program will include four months of weekly classes on weight loss, diet improvement, increasing physical activity, and behavior change followed by an eight-month maintenance period with monthly group meetings, biweekly health related text messages, and continued support of the health education teams. The work environment will be supportive of these changes with management advising and promoting the program, allowing staff time to participate, providing staff as health educators, allowing space for classes, testing, and other study activities, covering some of the costs of testing, and making changes in canteen food offerings to adhere to the recommendations of the program.

The program evaluation will use mixed methods techniques to assess program acceptability, impact, and effectiveness. Although the goal of the program is to benefit employees, the program evaluation includes measures such as cost-effectiveness, changes in employee absenteeism/presenteeism and qualitative assessments of employee views of the program that will be beneficial to employers using or considering this program for their worksite. In addition, the acceptability and impact of the program will be measured from the perspective of multiple stakeholders – program users, employees at the worksite, and worksite management. Understanding the program outcomes and acceptability from these multiple perspectives will provide rich data

for making recommendations for sustaining and disseminating the program.

Although this study will be conducted in India, the results will be applicable to workers in other settings, including the U.S. (see Foreign Justification). Asians, including Asian Indians, are the fasting growing ethnic group in the U.S., and between 2000 and 2010 the Asian Indian population increased by 67.6%.[71] Furthermore, several of the companies committed to this trial (the TATA group, L&T, and Cognizant) have locations worldwide, including offices in America, and these sites would be ideal locations for first phase dissemination. In addition, lessons learned in this study would benefit U.S. companies with worksites in India.

Approach

This study will use a pre-post design at eight diverse worksites to assess program implementation, fidelity, effectiveness, and impact on study participants, workers, and the worksite. There will be no control group because there is already convincing evidence from randomized trials[8,9,17,53,58,72] that lifestyle intervention is beneficial for preventing diabetes and diabetes-related complications. Although randomized controlled trials provide the most robust evidence for effectiveness, meta-analyses have shown that the results of non-randomized, effectiveness studies do not systematically differ from the results given by randomized controlled trials of the same treatment.[73,74]

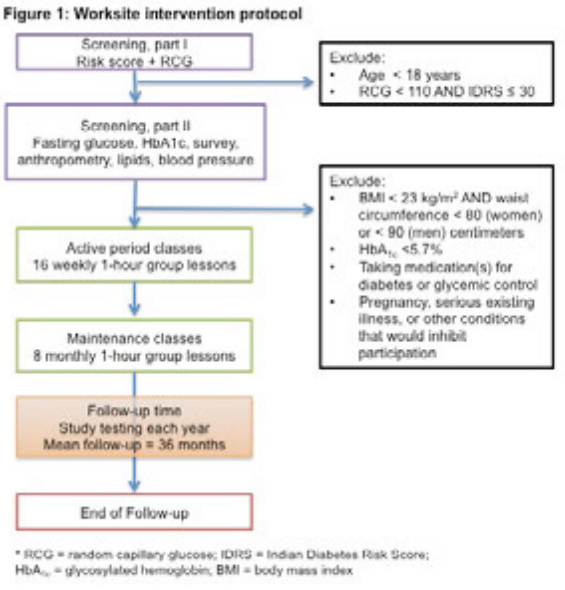
Intervention

The lifestyle intervention will be conducted at eight worksites (see Table 1 and letters of support). These worksites have large workforces (1,500-50,000 employees) and represent a range of industries with locations across India. An overview of activities to be conducted at each worksite are shown in Figure 1.

Table 1: Demographic Overview of Study Sites

Company name	Location	Type of Industry	Number of Employees	Employee Age-range	Percent Women
Chennai Petroleum Corporation Ltd	Chennai	Oil Refinery	1,500	30-55	1-2%
L&T Infotech	Chennai	Technology and Business Services	3-5,000	20-50	30-35%
Cognizant Technology Solutions	Chennai	Technology and Business Services	50,000	25-55	30-40%
Rourkela Steel Plant	Rourkela	Mining and Steel Manufacturing	18,000	19-65	26%
TATA Consultancy Services	Chennai	Technology and Business Services	50,000	25-55	30-40%
Bokaro Steel Plant	Bokaro	Mining and Steel Manufacturing	19,000	19-65	31%
Bhilai Steel Plant	Bhilai	Mining and Steel Manufacturing	30,000	19-65	27%
TATA Steel	Jamshedpur	Mining and Steel Manufacturing	36,418	19-65	29%

Study Sample: Inclusion criteria are: aged ≥18 years; overweight or obese using World Health Organization defined South-Asian cut-points: BMI≥23 kg/m^2 and/or waist circumference≥90 cm for men and ≥80 cm for women;[75] have prediabetes (HbA_{1c} of 5.7-6.4%) or diabetes (HbA_{1c}≥6.5%); not currently taking any diabetes medications; not pregnant or breastfeeding; and without history of heart disease, current serious illness, or conditions which would impede participation in an unsupervised physical activity and diet change program.



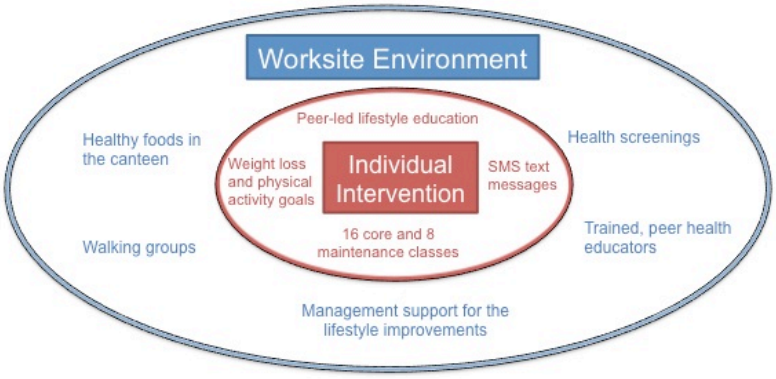
Eligible individuals will be identified using a two-phased screening program at each worksite. All interested workers at the study site will be allowed to attend the Phase 1 screening visit and will be provided with a health report describing the results of the screening visit to share with their doctor. Phase 1 Screening will entail a short questionnaire with questions on demographics and general health behaviors and the Indian Diabetes Risk Score (IDRS) questionnaire, anthropometric measurements (height, weight, and waist circumference), and random capillary glucose (RCG) measurement. IDRS is simple to administer, includes only four questions (on age, waist circumference, physical activity, and family history of diabetes), is a reliable instrument for identifying individuals with diabetes and prediabetes, and can be easily used in the field and during program dissemination.[76,77] Individuals with a RCG≥110 mg/dl or IDRS > 30 will be invited for Phase 2 Screening. Phase 2 Screening will include a fasting blood draw to measure HbA_{1c}, glucose, and plasma lipids, blood pressure measurement, anthropometric measurements (height, weight, waist circumference), and a study questionnaire. The screening program will need to be low-cost and easy to incorporate into a workplace setting, while still successfully identifying patients with prediabetes and diabetes. HbA_{1c} testing is easy, can be done on a non-fasting individual, is relatively inexpensive, and is recommended as a diagnostic tool for diabetes and prediabetes by expert groups including

the American Diabetes Association.[41,78] Eligible and consented individuals will be enrolled in the lifestyle education program, and all individuals attending screening will receive a report of their results. Any individual presenting with results indicative of a health condition, including diabetes, will be referred to their primary care or company physician for clinical follow-up.

Preliminary data: D-CLIP [clinicaltrials.gov #NCT01283308, Emory University and Madras Diabetes Research Foundation (MDRF) investigators] is an on-going, translational, diabetes prevention study comparing standard lifestyle advice to a step-wise, culturally tailored program (group lifestyle classes plus metformin for participants not responding to lifestyle change alone) among 602 people with prediabetes in India.[25] D-CLIP was developed based on the DPP Curriculum.[79,80] Early unpublished D-CLIP results are promising. The participation rate for intervention classes was high (83%), and loss to follow-up was low (9%). At eighteen months, lifestyle participants had significantly greater reductions in weight (-1.7 vs. -0.8 kg), BMI (-0.6 vs. -0.3 kg/m^2), and waist circumference (-2.7 vs. -2.0 cm) than controls. Additionally, intervention participants showed greater improvements in systolic blood pressure, triglycerides, and HbA_{1c}; 21% of controls achieved improvement in two or more of these risk factors while 33% of intervention group did so. Similar to previous studies showing that weight, BMI, and waist circumference reductions significantly predicted diabetes risk reduction in lifestyle interventions,[81] preliminary D-CLIP analyses show a 51% relative risk reduction in diabetes incidence in intervention participants compared to controls. The effects of the D-CLIP intervention were consistent across sex, age, income, education, and baseline BMI and glucose intolerance.[82]

Recommendations for improving the Indian diet to better prevent diabetes and reduce cardiometabolic risk factors will be developed based on the work assessing the value of improving food quality of the Global Nutrition and Epidemiologic Transition (GNET) initiative at Harvard University and MDRF. For example, a small crossover trial of substituting brown rice for white rice for five days, found that brown rice lowered glucose levels by 19.8% and fasting insulin by 57%.[40] GNET studies in other populations further support benefits of improving carbohydrate quality.[38] Moreover, studies of acceptability of brown rice in India indicate that well-informed, sensory trained panelists readily accepted brown rice,[32] but translating this intervention to the public will require additional education and training.[27]

Figure 2: Components of the Lifestyle Intervention at the Individual and Worksite Environment Levels



The Intervention Package: The intervention package will include both an individual intervention (the lifestyle curriculum) and supportive changes to the worksite environment (see figure 2). The individual components will benefit those employees enrolled in the lifestyle education program, while any changes to the work environment would benefit all employees.

The lifestyle education program will be based on the curriculum developed and tested in D-CLIP, modified to suit the workplace environment and based on feedback from focus group discussions (FGD) conducted at the end of D-CLIP lifestyle classes, experiences of the study team, and recommendations of key worksite contacts (e.g., worksite health workers and members of a study guidance committee made up of worksite managers, a worker representative from each site, and industry leaders). Core components of the intervention package include:

- Eligible participants will be divided into classes of 10-12 people, and each class with be paired with one trained lay educator and a professional health educator from the study staff (the health education team). Both individuals will participate in training programs for delivery of health education with a focus on teaching healthy behaviors, leading by example, providing support, and facilitating group interactions. The professional health educator will provide continued on-site training and supervision for the peer health educator, team-teaching the first 2-3 lessons and then observing classes until the peer educator feels confident leading the classes alone. Various research studies have shown that using trained community health workers for patient management and peer education can be as effective as using health professionals[18] and is a low-cost and sustainable method for improving patient outcomes, increasing knowledge, and preventing poor health outcomes (e.g., in a program of CVD screening and prevention in rural India[83] and a lifestyle modification program for low income Hispanic Americans with T2DM[6]). Each site will employ one professional health educator and identify two-three lay educators from among the staff at the site. Lay educators will be employees of the worksites, and the worksites have agreed to allow these

employees to perform their study-related duties as part of their workday. The training program will be developed collaboratively with the Diabetes Training and Technical Advisory Center (DTTAC, http://www.dttac.org, see Letter of Support) at Emory University, the group responsible for developing and delivering the train-the-trainer program for helping scale the national DPP in communities across the U.S. (http://www.cdc.gov/diabetes/prevention/training.htm).

- The curriculum includes 24 sessions: sixteen core sessions weekly during the first four months of the program followed by eight monthly maintenance sessions. Each class will last one hour and will include: (a) 20 minutes where the health educator will present a scripted lecture covering a health topic; (b) 20 minutes of group-based activities, for example role-playing exercises and group discussions; and (c) 10 minutes of physical activity training (see below). Topics to be covered include: importance of maintaining a healthy weight for diabetes prevention/maintaining healthy blood glucose levels, eating a healthy diet, increasing physical activity, overcoming barriers, and building social support. At the start of each session, participants will be weighed to chart their progress. All classes will be conducted at the worksite during the workday (e.g., over the lunch break, at the beginning of the day), depending on worksite and participant needs.
- During the maintenance period (eight months beginning after the active period classes have ended), participants will attend a once monthly class covering topics such as maintaining healthy behaviors long-term, overcoming decreases in motivation, and educating others on healthy lifestyle behaviors. Maintenance classes will be supplemented with biweekly SMS text messages providing lifestyle advice, tips, and encouragement. The messages to be used were developed as part of a health promotion program designed by several partners on this project.[84] During long-term follow-up (one year after beginning lifestyle classes through year five), the health education team will hold small group refresher sessions quarterly.
- Participants will be given two study goals to achieve during lifestyle classes which are identical to those used in the DPP and D-CLIP studies:[25,80] increase physical activity to at least 150 minutes per week of moderate level activity and lose at least 7% of their baseline body weight (via diet and activity changes).
- Since formal exercise is not a cultural norm in India, it is important to train participants on exercise safety and technique. These topics will be covered in the lessons, and at the end of each lecture, participants will learn one-two new stretching or strength training exercises. During the D-CLIP trial, participants attended weekly exercise classes, which were well received by study participants (unpublished qualitative data); however, a two-hour weekly class seemed difficult to implement and sustain in a work-based setting. Instead this training will be incorporated into the classes and participants will be trained on goal setting, planning, and overcoming barriers to help with implementing exercise daily. The lay health educators will also lead optional walking groups several times per week, open to participants and other employees.
- Participants will be given the knowledge and tools necessary to improve their diet quality and quantity. They will be taught about portion sizes; monitoring hunger/fullness; increasing fresh fruit (not fruit juice) and vegetable intake, avoiding sugar sweetened beverages, choosing whole grains more often while reducing consumption of refined grains; choosing healthier fats for cooking; minimizing consumption of fried foods; choosing healthier protein sources; reducing sodium; and reducing total fat intake, when necessary, as a way to manage caloric intake. These guidelines follow decades of research on healthy diets by co-Investigators Willett, Spiegelman, and their colleagues.[85-88] To facilitate these changes, the study team will work with the worksite canteens to create healthy options at all meals.
- Individuals will be encouraged to keep food and activity dairies throughout the course of the study. Record keeping has been shown to be an important predictor of success in weight loss programs.[89]

Adaptive elements of the intervention (components that can be modified to suit individual worksites) are included so that worksites and health educators can tailor the program to the needs of participants and the work environment. These are:

- Timing and composition of classes: Classes can be held anytime during work hours so that each worksite can choose class schedules that best suit the work environment and participants. The composition of classes (e.g., single sex, divided by type of job, etc.) will be determined at each site following discussions with management and employee representatives.
- During each lesson, the health education team will be able to tailor the discussion and activities during the second half of the class to the study participants and worksites. For example, on a lesson on overcoming barriers, participants may want to discuss different issues specific to the worksite or types of participants.
- Flexibility in what foods to offer at canteens: we will work with each study site's management and canteen staff to help facilitate the incorporation of more healthy food items, tailoring the recommendations to account for regional differences in diet.

- The lifestyle program is designed to increase self-efficacy, teach individual goal setting and attainment, and empower participants to make health decisions that they feel fit within their lives and are important to them. Participants are given choices for how to reach study goals, and then can work towards these goals choosing the tools that are right for them individually.

To minimize Type III error (poor or inadequate implementation of the intervention), an assessment of the fidelity to the intervention components will be conducted (see Data Collection and Data Analysis). Methods to maximize fidelity between study sites include: (1) The intervention has been previously field tested as part of a large randomized controlled translation trial (D-CLIP[25]) which included qualitative and quantitative assessments of the intervention delivery. The worksite intervention program will be created based on the results of the D-CLIP program assessment. (2) We will form a study guidance committee, chaired by the Chief Medical Officer of Tata Steel (Dr. Madhusudanan), which will include a member of senior management and an employee representative from each site as well as business organization leaders, to advise the study team on optimal conduct of the study. This group will be instrumental in making recommendations for program maintenance and dissemination after the trial. In addition, this group will have quarterly calls to update the study guidance committee on study progress and maintain involvement and investment in the intervention program by worksites. (3) Members of the health education team, including both staff and lay health educators, will participate in standardized training, including training on delivering the intervention, managing group interactions, and program content. To minimize intervention drift[90] over the course of the program, all health education team members will participate in a monthly conference call, which will include booster training sessions and problem solving discussions. (4) Study manuals and protocols for screening, program delivery, and data collection, entry, and reporting will be provided to all study personnel and sites in the preferred language of the worksite. A multilingual team drawn from the study staff at PHFI, MDRF, and Emory will oversee translation of all materials, including back-translation to check and maintain consistency between versions of the documents. (5) The lecture part of each lifestyle class will be scripted and the group activity will have general guidelines to ensure that key messages are conveyed at each study class. (6) The coordinating center will conduct annual monitoring visits at each worksite.

Data Collection

This study will utilize mixed methods to assess program implementation (see table 2).

Table 2: Data Collection and Analysis by Aim

Aim	Outcome being measured	Method
1	Adoption of the program (lifestyle class components and/or worksite environmental changes) by worksites and participants	Qualitative
1	Adoption and adherence to the program (lifestyle class components) by participants by measuring changes in weight, diet and physical activity	Quantitative
1	Fidelity to program core components	Qualitative
1	Fidelity to the program assessed through checklists for health education team and observations/records of changes made to canteen foods	Quantitative
1	Acceptability of the program (lifestyle class components and/or worksite environmental changes) to the workers, management teams, and participants	Qualitative
2	Lifestyle education program effectiveness through changes in the primary outcome, a composite risk factor score including blood pressure, triglycerides, and HbA_{1c}	Quantitative
2	Changes in secondary outcomes including rates of diabetes incidence and regression to normoglycemia, changes in the prevalence of 1-3 risk factor goals (improvements in triglycerides, blood pressure, and/or HbA_{1c}) from baseline to end of study, and changes in anthropometry, lipids, and fasting glucose	Quantitative
3	Impact of the intervention on worker satisfaction in their jobs and the company	Qualitative
3	Impact of the intervention on workers and the worksite specifically cost associated with the program, cost-effectiveness, reports of absenteeism and productivity, health status and quality of life	Quantitative

Qualitative data collection (Table 3) will include a maximum of 32 FGD and 456 interviews (96 with supervisors, 200 with dropouts, and 160 with employees), providing rich qualitative data across and at each worksite. Qualitative data collection in each category and at each time point will continue until data saturation is reached (when no new information is being shared by participants).[91] Participants in all categories will be recruited with the goal of identifying information-rich individuals who represent diverse groups at the worksite (different sexes, age groups, positions, etc.). Interviews will be used when understanding individual views are important (e.g., study dropouts may have individualized reasons for stopping the program) or when collecting data that individuals may be unwilling to share in a group (e.g., feedback on employee satisfaction, reports of worksites not implementing program components). FGD will gather community (in this case participant) level views on the intervention. All interviews and FGD will be conducted by a trained interviewer/moderator who is of the same gender as the participants to retain group homogeneity, thereby promoting a more open

discussion.[92] The discussions will be guided using semi-structured interview/FGD guides, which will be informed by the D-CLIP study and made culturally appropriate for the target individuals and setting. Guides will be pilot tested, refined, and translated before use in the field. FGD and interviews will be conducted in the preferred language of participants and will be audio-recorded with a digital recorder, transcribed verbatim, and translated into English. To enable comparisons between subsets of those interviewed (e.g., different age groups, etc.), participants in the qualitative research will fill out a brief demographic survey.

Table 3: Qualitative Data Collection Tools

Method	Participants	Maximum Number and Timing	Recruitment Method	Topics
In-depth Interviews	Managers/ supervisors	4 per worksite: 2 high-level managers (make decisions about the worksite environment) and 2 supervisors (provide direct supervision to employees) in years 1, 3, and 5	Worksite will be asked to provide a list of managers and supervisors. The study team will contact people from the list until interested participants are identified.	• Perceptions of diabetes and overweight/obesity (year 1, 3, 5) • Worksite's role in health promotion (years 1, 5) • Perceptions of the program (years 3, 5) • Changes made at worksite due to the program and feelings around these changes (years 3, 5) • Suggestions for improvements and future programs and for independent implementation and sustaining of program at worksites (year 5)
In-depth Interviews	Program drop-outs	25 per worksite conducted throughout the intervention period	Individuals who drop out of the program will be contacted for interviews.	• Perceptions of obesity/overweight, weight loss, diet change, and exercise • Reasons for drop-out • Likes/dislikes about the program • Suggestions for improvements
Focus group discussions	Program participants	2 groups of men and 2 groups of women at each worksite at the completion of the intervention	Health education team will identify information rich study participants.	• Perceptions of obesity/overweight, weight loss, diet change, and exercise • Likes/dislikes about the program • Suggestions for improvements
In-depth Interviews	Employees at worksite	10 program participants/10 non-eligible employees per worksite in years 3 and 5	Flyers will be placed around the worksite (break rooms, announcement boards, etc.) asking individuals interested in participating to contact study staff.	• Awareness and views of program • Perceived support for program by management • Questions to assess fidelity to intervention by worksites and health educators • Changes made/sustained at the worksite during the program • Suggestions for how worksite could promote healthy lifestyles

Quantitative data collection (Table 4) will occur at study-testing visits at baseline and every twelve months after lifestyle classes begin. Whenever possible, validated study instruments will be used. The primary outcome assessing program effectiveness (Aim 2) will be a composite of achieving two or more cardiometabolic risk goals; participants will be scored on the number of risk factors they improve on (0-3) with success delineated by a HbA_{1c} decrease ≥0.5%; a systolic blood pressure decrease ≥5 mm Hg; and a decrease in plasma triglycerides ≥10 mg/dl. This outcome was selected for three reasons: other risk scores for CVD (e.g., the Framingham Risk Score) do not perform as well in South Asian populations;[93] these risk factors are commonly measured by clinicians, so the results are clinically appropriate; and the composite outcome allows for individual variation in risk factor profiles and the ability of individuals to reduce different factors (e.g., an individual with a baseline HbA_{1c} of 5.8% is unlikely to reduce this risk factor by 0.5%, but may succeed in reducing triglycerides or blood pressure).

Table 4: Quantitative Data Collection Tools

Variable of interest (test)	Outcome of test	Timing S	B	A	FU
Demographics and Lifestyle Behaviors					
Demographics (SQ)	Describe study population	X	X		
History of smoking (SQ)	Smoking status and cessation rates		X	X	X
Global Physical Activity Questionnaire (GPAQ)[94]	Baseline and changes in physical activity		X	X	X
Dietary intake (food frequency questionnaire)	Study specific food frequency questionnaire on dietary intake of foods targeted in the intervention		X	X	X

Variable of interest (test)	Outcome of test	Timing S	B	A	FU
Dietary behaviors (SQ)	Prevalence of diet-related behaviors (e.g., reading nutrition labels, eating at restaurants, measuring portions, etc.)		X	X	X
Weight loss history (SQ)	Weight loss history including number and success of past attempts, methods used, etc.		X		
Quality of life (EQ-5D)	Baseline and changes in quality of life		X	X	X
Self-reported health (SF-12 and SQ)	Health status, recent health events and medication use (type and dosage of all prescription and over the counter medications and herbal remedies)		X	X	X
Worker satisfaction (SQ)	Questions assessing worker satisfaction with worksite, number of days missed work, self-described levels of productivity		X	X	X
Health-related outcomes					
Glycemic control (HbA_{1c})	Identify eligible participants and assess improvement	X	X	X	X
Glycemic status (venous fasting plasma glucose)	Assess effects of program on glycemic status		X	X	X
Height and weight (stadiometer; weighing scale)	Baseline and changes in weight (kg), BMI (kg/m^2) and percent overweight/obese	X	X	X	X
Waist circumference (non-elastic tape measure)	Baseline and change in waist circumference	X	X	X	X
Blood pressure (automated blood pressure machine)	Baseline and change in blood pressure and hypertension	X	X	X	X
Lipid profile (fasting venous triglycerides, HDL, LDL)	Baseline and change in plasma triglycerides, LDL-cholesterol, and HDL-cholesterol	X	X	X	X
Measures of Program Cost					
Cost questionnaire (SQ)	Participant cost of diabetes care and medicines for diabetes, blood pressure, and lipids, prevention, and complications		X	X	X
Program costs (data collection from worksite, study records)	Cost (monetary, person time, etc.) of delivering program			X	X
Worksite productivity (worksite records)	Absenteeism, presenteeism, productivity, turn-over		X	X	X
Program Fidelity and Acceptability					
Weekly checklists for health educators	Checklists of required and optional activities for health educators to fill out weekly		X	X	
Participation in lifestyle intervention (attendance records, number of diet/activity records turned in)	Program attendance and adherence		X	X	
Participant feed back (SQ)	Acceptability of program components and suggestions for improvement			X	X

S = Screening; B = Baseline; A = Annually throughout follow-up period; FU = End of follow-up; SQ = study questionnaire; HbA1c = glycosylated hemoglobin; BMI = body mass index; LDL = low-density lipoprotein; HDL = high-density lipoprotein

Data Analysis

When appropriate, all data analysis will be conducted for the entire study and individually by site. Qualitative data will be comprised of the translated, verbatim transcripts of the in-depth interviews and FGD. Textual data will be managed using the MAXqda10 (VERBI Software, 1989-2012). A codebook for each set of qualitative data will be created, tested for inter-coder reliability, and used to code the transcripts. When appropriate, qualitative data will be used to modify and improve intervention components and guide selection of adaptable components at each site. De-identified quantitative data will be entered into Microsoft Access databases. Range checks, disallowing invalid values, and adaptive double entry, along with regular data audits will ensure the accuracy of the electronic data. Data analysis will be conducted using SAS primarily. Descriptive analysis will be performed for all variables and outliers will be investigated for data errors. A probability of <0.05 will be considered statistically significant for all tests.

Aim 1: Success of program implementation will be assessed as follows:

a) Program Adoption: Program adoption will be measured by quantifying participation in the program and success in reaching the goals of the lifestyle education program (weight loss, increased physical activity and diet improvements). Participation will be measured by calculating the percentages of total employees agreeing to screening, agreeing to participate in the program, and enrolling in lifestyle classes. Attendance records for study classes and other activities and numbers of diet/activity tracking booklets turned in for review by the health educator will be reviewed to determine percent attendance at each class and at classes overall. Physical activity [in Metabolic Equivalent of Task (METS)/day] will be quantified using the Global Physical Activity Questionnaire (GPAQ).[94] Diet changes will be quantified through a study-specific food frequency questionnaire, which will include food items that participants are encouraged to eat more or less often, as well as questions on diet-related behaviors (e.g., reading food labels, measuring portion sizes). A healthy diet score will be calculated from the food frequency questionnaire and other diet related

questions.[95,96] Changes in weight, BMI, waist circumference, physical activity, and diet score over time will be modeled using generalized estimating equations for clustered, repeated measures data,[97] and heterogeneity in the intervention effect over time on each outcome by education, income, gender, age, baseline BMI category (normal weight, overweight, and obese), baseline physical activity, and baseline diet score will be evaluated.

b) Program Fidelity: Program fidelity will be determined by measuring study-affiliated activities by the health education team, study canteen, and worksite management, changes in the worksite environment, and management support for the program. Checklists will be created for each study class and between-class activities (e.g., reviewing food and activity records, interactions with participants) to gather self-reported fidelity by health educators. Reasons for non-compliance will be assessed during monthly calls with the health education teams. To assess compliance to recommendations to provide healthy food options in the canteen, twice per year a member of the study team not affiliated with the worksite will do a random audit of available canteen foods and daily canteen menus will be collected and analyzed to determine amounts of and changes in number and types of healthy foods offered. In-depth interviews with employees (both program participants and non-participants) and managers/supervisors will be conducted to assess changes made at the worksite during the program.

c) Program acceptability: We will assess program acceptability through in-depth, semi-structured interviews with managers and supervisors at the study sites, lifestyle program dropouts, and employees at the worksite (both program participants and ineligible/uninterested employees) and through FGD with program participants. Qualitative data will be supplemented by multiple choice and yes/no questions included on participant questionnaires asking about specific components of the lifestyle intervention (e.g., “How often do you choose brown rice instead of white rice?” or “Do you keep diet records?”). Percent reporting various answers and comparisons of percentages will be calculated.

Dr. Hennink, an expert on qualitative methods, particularly in low- and middle-income country settings,[98,99] will provide expertise and guidance for the collection and analysis of all qualitative data. Drs. Weber, Willett, and Spiegelman also have experience with qualitative data.[27,34,39,100] For qualitative data collected for parts b and c above, we will conduct a thematic analysis [91] to describe program acceptability and fidelity at different levels (program participants, worksite, and worksite management) and summarize suggestions for improving, sustaining, and disseminating the program. This analysis will include: (a) a *descriptive analysis* to identify core themes across sub-groups (e.g., managers, dropouts, women only, younger participants, etc.) and (b) a *comparative* analysis between groups to distinguish the context of each issue and different perceptions of barriers, facilitators, sustainability, etc. In addition, if the data is sufficiently rich, we will conduct a grounded theory analysis[101] to explore experiences and qualities of worksites which predict better fidelity to the program.

Aim 2: Statistical analysis of intervention impact: A generalizing estimating equations (GEE) framework for clustered data[97] will be used to assess the statistical significance of any observed intervention effect on the endpoints. For the primary endpoint, the dependent variable will be the indicator for whether the study participant is at two or more cardiometabolic risk factor reduction goals at the end of the 3 year follow-up period, minus the expected probability of this endpoint in the absence of an intervention, to be taken as 21% as observed in the D-CLIP[25] control group. An exchangeable working correlation matrix will be used to incorporate the clustering within the 8 work-sites, with a log link and binomial variance specified. The exponentiated point and interval estimates from the intercept of this model will quantify the intervention effect, and the p-value associated with the model’s intercept will provide a measure of the statistical significance of the findings. A similar GEE approach will be used to estimate and test the significance of intervention effects on secondary endpoints. For continuous markers, such as systolic blood pressure and HbA_{1c}, the post- to pre- within-participant difference will serve as the dependent variable in a GEE model as above, with the identity link function and the distribution specified as normal. The change scores will be evaluated for outliers, and analysis will be repeated with and without extreme outliers. For the cumulative incidence of diabetes at end of follow-up, participants will be coded as one if they satisfy the diabetes definition at end of follow-up and 0 otherwise. A Cox proportional hazards regression model for the diabetes incidence rate will also be considered, and if dropout or loss to follow-up are non-negligible, causal methods for adjusting for dependent censoring will be applied.[102] A similar approach will be used to assess regression to normoglycemia. We will consider worksite-level covariates in multi-level models to examine how these aspects might affect findings. Additional secondary endpoints will be considered (e.g., changes in being at 1, 2 and 3 CVD/T2DM risk factor goals). Although the study is not powered to detect it unless quite large and although no effect modification is expected, we will assess the presence of effect modification by calculating intervention effect estimates stratified by potential modifiers, such as gender, age, marital status, socio-economic

status, and assess the statistical significance of any effect modification observed by calculating a cross-product term between the potential modifier and the intervention, using a robust score test to assess the significance of this term.[97] To assess the causal effect of the intervention adjusted for bias due to non-adherence and loss to follow-up, marginal structural models will be fit, embedded around the analysis approaches outlined above.[103] The study statistician, Dr. Spiegelman, has substantial experience fitting these causal models to adjust for time-dependent confounding and dependent censoring, e.g.[104-107].

Aim 3: Impact of the intervention on workers and worksite: Qualitative data from interviews with employees on job satisfaction and views of the company and worksite will be described using the thematic analysis methods described in Aim 1. The analyses below are aimed at helping stakeholders that might consider adopting this intervention program to be fully informed of the upfront (fixed) and recurring (variable) costs to deliver the intervention and the potential return on investment (ROI). We will use an employer/societal perspective and will report cumulative and per-site estimates. Analyses for this aim will include:

a) Estimating total costs to deliver the intervention: we will estimate average fixed and variable costs of delivering the lifestyle change program at worksites in India. Specifically, we will collect cost data from each worksite regarding components of the intervention: 1. Screening for high-risk individuals; 2. Delivering the individual lifestyle education program (per employee enrolled), which include labor costs for lifestyle coaches and classes and education materials; and 3. Changing the work environment (per campus and per 1,000 employees), which include costs for subsidizing purchase and preparation of healthy foods, as well as any capital costs (e.g., gym facilities, walking paths).
b) Staff productivity (absenteeism; presenteeism) and indirect costs: Absenteeism will be calculated from worksite attendance records. To assess presenteeism, we will administer a questionnaire that captures performance of employees (specific markers of productivity for each worksite and employee function). We will calculate indirect costs (monetary value of lost productivity) using the human capital approach (multiplying combined days lost to absenteeism plus presenteeism by salary of different occupational roles). Changes in these measures over the course of the program will be modeled for each study site and for all study sites using mixed methods models.
c) Health status and healthcare utilization of employees: The self-reported health status of the employees participating in the lifestyle intervention will be determined using the SF-12 questionnaire and study questions on health status, hospitalizations, and medication use. Changes in health status and utilization will be modeled over time and compared across worksites, levels of program adherence, and baseline health status (e.g., comparing those with diabetes and prediabetes).

ROI (cost-benefit and cost-utility analyses): To estimate potential ROI for worksite leaders, we will calculate an overall cost-benefit in monetary terms. To do this, we will identify the costs incurred by employers in the years prior to the study and costs during the study (incremental investments). We will then identify total benefits (cumulative indirect costs) prior to the study and during the study (annually, and at completion). We will consider: 1. Cost-benefit (ratio of incremental costs to change in productivity) without any health expenditures (assumes employer doesn't pay for employees' health care); 2. Cost-benefit that includes aggregated medical (physician consultations, medications, diagnostic tests, inpatient stays) and lost productivity costs, which assumes employers pay for employee healthcare; and 3. Cost-utility ratio (net costs to net utility: costs of intervention – average costs in previous years / utility of intervention – utility of control). To calculate utility, we will use the 12-monthly health utility measure, the quality adjusted life year (QALY), which is calculated as the sum of mean survival time [life years] x utility scores at 12, 24, and 36 months. We will report 12-, 24-, and 36-month costs per QALY.[108] If the intervention is successful, we will also compare modeled long-term cost-utility of the intervention and usual care using Markov Chain Monte Carlo estimation techniques, controlling for age, gender, and risk factor prevalence under different plausible scenarios for how these may evolve over time.[109] We will compare this to reference points from the literature – e.g., ceiling ratios for costs per QALY that are less than three times GDP per capita[110-112] are considered cost-effective (India's 2013 GDP per capita was $3,990; threshold: ≤$11,100 per QALY).[113] We will use sensitivity analyses to examine the effects of varying discount rates, costs of the intervention, and effectiveness. Drs. Ali and Narayan have expertise in economic analysis[114-123] and will consult with Dr. Ping Zhang, health economist at CDC, as needed.

Sample Size Selection: This worksite-clustered before-after design of 8 worksites with at least 250 eligible and enrolled participants per site and no more than 20% loss to follow-up (LTF) after 3 years will have 93% or more power to detect an estimated difference between the percent of participants at 2 or more CHD risk factor goals after 3 years of follow-up, the primary effectiveness endpoint of this trial, of 33% or greater, compared to the comparable D-CLIP[25] percentage of 21%. The 20% 3-year LTF rate is likely conservative, as only 9% of D-

CLIP participants have been lost to follow-up after a mean of 30 months. Similarly, the D-CLIP comparative percentage of 21% is likely conservative, because the D-CLIP control group also experienced a minimal intervention that included meeting with a physician and a dietician, attending two classes (a lecture on diabetes prevention through weight loss and diet change, and an exercise class), and receiving handouts reinforcing prevention of T2DM. Thus, compared to a community control receiving none of these services, the D-CLIP group would be expected to have a higher percentage at or exceeding two goals, compared to the community standard. In addition, power in this study is excellent for numerous secondary effectiveness endpoints of considerable interest, including 90% power or more to detect a decrease of 2mmHg or greater in systolic blood pressure (ρ=0.10, IIS), 95% power or more to detect a decrease in HbA_{1c} of 0.14% or greater (ρ=0.10, IIS), and nearly 100% power to detect a reduction in diabetes incidence of 30% or greater among the 2/3 of the study participants with prediabetes at baseline screening, compared to the baseline rate of 0.07/year,[124] otherwise under the same assumptions as the primary endpoint calculation.

All qualitative data collection will continue until data saturation is reached. The maximum number of groups/interviews to be conducted was selected based on prior experiences of the research team, in particular the number of interviews/FGD required to reach saturation in the D-CLIP trial. The maximum number of program dropouts to be interviewed (25 per site) was selected because this corresponds to half of the number expected to withdrawal from the program if maximum loss to follow-up of 20% occurs. The number of FGD (4 per worksite) will include, assuming ideal group sizes of 8-12 people, 32-48 people, approximately 12-20% of the lifestyle intervention participants, which should be a sufficient cross-section for describing the experiences and opinions of the participants. The numbers of other interviews (at two time points: 4 managers/supervisors, 10 participants, and 10 non-participants at each worksite) were selected based on estimates of numbers needed to reach saturation while maintaining a manageable number of interviews for study staff.

Timeline

The study timeline is shown in Table 4. The study will last five years, with one year for planning and training of staff. Screening and enrollment of intervention participants will occur on a rolling basis with two worksites starting screening every month beginning in month 13 of the study. Screening at each site will last for four months. During the final month of screening at each worksite, the first lifestyle classes will begin and new classes will be added as sufficiently sized groups of eligible employees are identified. Mean follow-up time (time from end of core lifestyle classes to end of study) will be 36 months. Data collection and analysis will be conducted throughout the trial and changes will be made if needed to improve and sustain the programs. Publication and presentation of results will occur in year two (for baseline results and study design paper), midway through the intervention (early results, results of post-intervention interviews/focus group discussions), and at the end of the study (final results). Dissemination plans are described below in Dissemination.

Table 5: Study Timeline

	Month of Study									
Activity	**1-6**	**7-12**	**13-18**	**19-24**	**25-30**	**31-36**	**37-42**	**43-48**	**49-54**	**55-60**
Project planning*	■	■								
Convocation and meeting of steering committee	■					■				■
Training of staff/lay interventionists, data collection teams		■								
Screening			■	■						
Intervention classes (core sessions)**				■	■					
Intervention classes (maintenance sessions)**			■	■	■	■				
Follow-up period#				■	■	■	■	■	■	■
Data collection and on-going analysis			■	■	■	■	■	■	■	■
Publication/presentation of results				■	■		■			■

**Project planning includes: finalizing intervention lesson plans and training materials for health educators, data collection tools (e.g., study questionnaires, interview/focus group discussion guides), and protocols; identifying and hiring/securing study staff and peer educators; and obtaining IRB approval for all study activities*

*** Start times for study sites and class cohorts (2 groups of 5 lifestyle classes each) are staggered slightly to minimize burden on study staff and study sites. Each class participates in core lifestyle classes for four months followed by eight monthly maintenance sessions.*

 # Follow-up period will include monthly maintenance classes and text messages send every other week with encouraging messages and tips on maintenance of healthy habits for eight months post-core lifestyle classes, twice per year small group meetings with health coaches (after the end of maintenance classes), annual testing, and continued availability of health coaches.

Study Team and Governance

This experienced and multi-disciplinary research team from two U.S. and two Indian institutions has already collaborated extensively on research in the areas of diabetes prevention, epidemiology, nutrition, and diabetes treatment (for example[25,32,33,40,44,69,125-127]). Dr. K.M. Venkat Narayan, a leader in diabetes and translational research, will act as study P.I. and chair of the study steering committee. Dr. Prabhakaran, director of CARRS at the Public Health Foundation of India (PHFI) in New Delhi will serve as the Indian P.I. and director of the

coordinating center, which will be held at PHFI. An intervention coordinating team, led by Dr. Ranjani will be based at the MDRF. The steering committee will include the study PIs, Emory investigators (Weber, Ali, Hennink), Harvard Investigators (Spiegelman, Willett), Indian researchers (Mohan, Ranjani, Jeemon) and representatives from the leadership at each worksite. The steering committee will meet at baseline, midpoint, and at the end of the trial, with subcommittees (e.g., intervention, data analysis subcommittees) forming and meeting by phone/virtually more often as needed. The Emory team brings expertise in diabetes translation, lifestyle change, qualitative research and economic evaluation; the Harvard team provides expertise in nutrition and statistical analysis; PHFI bring expertise in multisite study coordination; and MDRF provide expertise on diabetes prevention and lifestyle intervention in the Indian context.

Sustainability, Dissemination, and Future Plans

A major focus of this project is to demonstrate full-scale sustainability at worksites across India, with further interest in translation beyond the Indian context. As part of the program, staff members at the sites will be trained in delivery of lifestyle education, providing healthy food options to employees, and motivating healthy decisions at the workplace. These efforts can be easily sustained by the worksites long after the trial ends and will be particularly appealing to management if shown to be cost-effective and able to increase productivity. The involvement of industry leaders and worksite managers and employees (the study guidance committee) in program planning and frequent interactions with health education teams, study participants, and management (allowing for rapid adjustments to the study protocol if needed) will ensure a program that is acceptable to the worksites and targeted to the needs of workers. The results of the trial will be used to tailor the program so that it can be disseminated in a way that is acceptable, feasible, and effective at other worksites.

The study guidance committee will contain industry experts who can help advise on how and where to disseminate the lifestyle program to create a healthier workforce. Initially dissemination efforts can focus on implementing the program at other worksites and units within the companies involved in this study (including those in the U.S.). If additional funds can be identified, we will also set up a program housed at PHFI or another Indian partner to provide advice and tools to companies and worksites wanting to implement lifestyle education programs for their employees. Results of the study, with links to available materials and manuals, will be published in scientific journals and on the PHFI and other websites related to study investigators. Press conferences will be organized to announce the program and study results to the media. We will also utilize available networks already formed between the business community and study investigators at PHFI and MDRF (e.g., Dr. Prahbakaran serves on the Expert Committee on Health at the PHD Chamber of Commerce and Industry) and with other contacts working to promote worksite fitness or chronic disease prevention (e.g., Arogya World http://www.arogyaworld.org). When appropriate, results of the study will be used to make recommendations or plan similar studies or programs in other countries including the U.S.

A number of additional analyses that have broad policy implications will be made possible upon study closeout. This includes analyses which strive to disentangle the separate effects of the intervention package components by using causal inference methods[128] to exploit non-adherence to elements of the intervention by individual participants and using external data (e.g., the ongoing longitudinal observational CARRS study[129] led by the PIs of this proposal and underway in some of the same cities in which this intervention will be conducted) as a comparator to the intervention effects, making it possible to adjust for confounding by contemporaneous secular trends, imparting this analysis with the flavor of a parallel group longitudinal design with an explicitly randomized control group. In addition, complementary empirical social network construction[130] and agent-based modeling approaches[131,132] could quantify the extent to which the intervention, or parts thereof, spreads to workers at the same worksite who were ineligible for the intervention and to family members and friends. Further predictive modeling of impact and cost effectiveness into the future can be conducted to investigate the extent to which the intervention can contribute to stopping or mitigating the growing Indian diabetes and CVD epidemics. With inputs appropriate in the U.S. or other country contexts, modeling can be conducted that would be relevant domestically and in other countries undergoing the nutrition/epidemiologic transition.[133,134] Finally, utilizing the data from this intervention as well as additional information, decision-makers in industry, health care delivery and government can be brought together for a systems dynamics exercise which can be used to map out the full set of societal benefits and risks of this intervention, and further estimate its effectiveness and cost-effectiveness.[135] We will seek separate funding for these complementary activities and attempt to secure them while the intervention is ongoing, in order to obtain the necessary auxiliary data contemporaneously.

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PROTECTION OF HUMAN SUBJECTS

1. Risks to Human Subjects

a. Human Subjects Involvement, Characteristics, and Design

This study is a trial of lifestyle interventions at the worksite for preventing diabetes and reducing cardiometabolic risk factors. The trial will include an individual intervention (lifestyle education classes) supported by worksite environment improvements. Program evaluation will include quantitative assessments of intervention class participants and changes at the worksite level and qualitative data collection from class participant and worksite managers and employees. The implementation and evaluation of such a trial can only be done using human subjects.

Throughout the study, participants will be treated with respect and reassured that they have the right to withdraw from the study at any time without any consequence for their usual care or their position at the workplace. Special care will be taken to ensure that company management does not exert undue pressure to participate in the study. Studies will conform to codes of conduct regarding: 1) data protection, 2) inclusivity of all sexes, denominations, and ethnic groups, 3) informed consent, and 4) confidentiality of individual information. Also, although no particularly hazardous interventions are anticipated in this project (phlebotomy and finger-prick blood glucose estimation are minimally painful), we will carefully monitor adverse effects of the program. Where deemed necessary, study respondents in need of medical attention will be attended to in the worksite health clinic or referred to the nearest appropriate facility for treatment. We are familiar with practices that minimize risk to participants and will endeavor to uphold all ethically honorable principles regarding human subjects participation. At each study site, the site coordinator will oversee the ethical treatment of all human subjects and data. All protocols, curriculums, consent documents, and data collection plans and instruments will be submitted for ethics approval by the Institutional Review Boards at Emory University and Harvard University and the Ethics Review Committees at PHFI and MDRF. The protocols will also be submitted to the health and safety officers at each worksite for approval.

The lifestyle classes will include 2,000 people across eight study sites (250 per site) with prediabetes or diabetes who are not taking glucose-lowering medications, as determined during study screening. This study will be conducted using a pre-post design without a control group. Given the strong evidence for the importance of healthy lifestyles and lifestyle changes for prevention of diabetes and management of diabetes, the study team felt it would be unethical to include a group not receiving the intervention. Worksite environment changes (e.g., offering healthy foods at the canteen, offering participation in walking groups) will impact all employees, regardless of participation in the intervention classes. The size of the workforce at each site varies, ranging from 1,500-18,000. Qualitative data collection (interviews and focus group discussions) will include both a subset of intervention class participants and a sample of managers/supervisors and employees at each worksite. Individuals in all study activities will be at least 18 years of age.

Lifestyle intervention participants will be overweight or obese with prediabetes or diabetes. Individuals with conditions where unsupervised diet change and physical activity would be counter-indicated will be excluded, but otherwise participants could have minor-moderate health issues. Since this is a working population, it is anticipated that most participants will be healthy. Eligible individuals will be identified using a two-phased screening program at each worksite. Phase 1 screening will entail a short questionnaire with questions on demographics and general health behaviors (smoking, alcohol use) and the Indian Diabetes Risk Score questionnaire, anthropometric measurements (height, weight, and waist circumference), and random capillary glucose (RCG) measurement. All workers at the study site will be allowed to attend the initial screening visit and will be provided with a health report describing the results of the screening visit, which they can share with their doctor. Individuals with a RCG≥110 mg/dl will be invited for Phase 2 Screening. Phase 2 Screening will include a fasting blood draw to measure HbA_{1c}, fasting glucose, and plasma lipids, blood pressure measurement, anthropometric measurements (height, weight, waist circumference), and a study questionnaire. Eligible and consented individuals will be enrolled in the lifestyle education program, and all individuals attending screening will receive a report of their results. Any individual presenting with results indicative of a health condition, including diabetes, will be referred to care by their primary care or company physician for clinical follow-up.

Participants for the qualitative efforts will be identified via study flyers (for employees), selected from an employee list (for supervisors/managers), or selected by the health educators (lifestyle participants and dropouts).

b. Sources of Materials

Data and specimens will be collected from subjects via questionnaires, focus group discussions, in-depth interviews, clinical evaluation, and minimally invasive phlebotomy. Collection and analysis of data are described in the sections Data Collection and Data Analysis within the research strategy section of this proposal. All participants will be approached at each data collection time-point, unless they voluntarily withdraw from the studies. All data collection uses well-established and validated questionnaires, clinical interview, and clinical assessment techniques. The collection of biological samples is minimally invasive and minimally painful. Data collection will be conducted at the worksites (the worksite health office for screening and study testing and a private office/conference room with a door for interviews and focus group discussions). Study participants will be identified by a study id number and compiled datasets and textual data will be cleaned of any personally identifiable information. A file linking the name and study id of participants will be available only to the site coordinators (for individuals at their worksites) and the project coordinator at the coordinating center.

c. Potential Risks

We consider the potential risks from data collection procedures to be extremely minimal. No invasive procedures are under consideration except for collection of finger-prick capillary and venous blood samples; these procedures are minimally invasive and voluntary. Some questions in the study instruments or during interviews could make participants uncomfortable. They will be informed of their right to refuse to answer any question. Appropriate precautions will be taken to avoid inflicting harm or risk to the well-being of subjects. If serious clinical conditions are uncovered, subjects will be referred for appropriate medical help, as per international standards.

The potential risks of participating in a lifestyle change program are also minimal. Changes in the diet and physical activity levels will be gradual, thereby minimizing the risk of injury (from exercise) or gastrointestinal side effects (e.g., from increasing fiber intake). Participants will be trained on exercise safety, including avoiding heat stroke, wearing proper footwear, and stretching.

Any potential adverse effects will be reported to appropriate individuals at the study sites (e.g., health and safety officers), the coordinating center, and both the study investigators and Human Subjects Committees at each collaborating institution (Emory University, Harvard University, PHFI, and MDRF).

Even though we have judged the potential for injury to research subjects from the proposed procedures to be minimal, all reasonable efforts will be made to further minimize these risks through the exclusive use of properly trained and educated research personnel and high-quality materials. As part of the informed consent procedure, individuals will be informed of their rights regarding injury sustained during study procedures and will be offered treatment for the injury according to prevailing local health policies. Detailed procedures for non-emergency and emergency referrals will be developed and implemented.

2. Adequacy of Protection Against Risks

a. Recruitment and Informed Consent

Recruitment procedures are described in the proposal in “Intervention” and “Data Collection.” Recruitment of trial participants will involve identification of subjects that fit the inclusion and exclusion criteria described under “Intervention.” All subjects approached for focus group discussion, interviews, screening, or the lifestyle education program will have the respective study explained to them in full (including the study objectives, all risks and benefits of participation, as well as contact details if further information is required and provisions for treatment/referral, as and where necessary) in their preferred local language, prior to seeking their participation.

Written informed consent will be obtained from all subjects at the first screening visit, upon enrollment into intervention classes, and before beginning any focus group discussion or interview. The details of the study, rationale for conducting the study, procedures with potential risks and benefits, and all provisions for contacting research staff, withdrawal from the study or treatment/referral (where necessary) will be explained. Subjects will be free to withdraw from the study at any time without prejudice or coercion and with no effect on their healthcare or position at the worksite. Consent forms and information sheets will be developed, translated and back-translated in all regional languages used in the participating worksites by a multilingual team drawn from

the study staff at PHFI, MDRF, and Emory and will be submitted for approval to the Human Investigations Committees of all collaborating institutions. The site coordinator or study staff laboratory technician will provide an oral overview of the consent documents, allow time for the individual to read the document, and answer any questions before asking the individual to sign if they consent to the study procedures. A copy of the consent form will be provided to the respondent to keep.

b. Protections Against Risk

Validated and previously approved protocols and instruments will be adapted to suit the research plans and context and will be internally and externally reviewed (by appropriate Institutional Review Boards [IRB]). Our experienced local South Asia investigators will additionally provide critical appraisal of all study tools to ensure content validity and cultural sensitivity prior to use.

The study will employ standard methods for protecting the confidentiality of research materials through the use of coded identification numbers on all materials, password-protected computer data files, and locked file cabinets in restricted-access buildings (at each network site, participating clinic and at the RCC at PHFI) for storing hard copies of interview questionnaires and other study materials. An additional off-site server for back-up of data will also be secured in a similar manner. Regular data transfer schedules, data back-up schedules and appropriate server security procedures (to ward off unauthorized data retrieval attempts) will be instituted.

All study personnel will be trained in procedures to minimize the potential for breaches of confidentiality, including but not limited to ensuring that all files are closed, that interviews are conducted in private settings, and that no conversations about individual study participants occur in public settings. Names and other easily recognizable identifiers will be removed from all questionnaires prior to data entry and will not be included in any electronic databases. Numeric study identifiers are included so that data from the several instruments may be linked; however, these are not meaningful to casual observers without access to the original study logs. All data files will be maintained under password protection at all times, at each participating site and at the coordinating center.

As shown in the tables below, the collaborating sites are all FWA certified and all co-investigators have certification in ethical conduct of research

Table A: FWA Certification and IRB numbers for Partner Institutions

Institution	FWA #	IRB #
Emory University, Atlanta	00005792	00000453
Public Health Foundation of India, New Delhi	00013596	00006658
Madras Diabetes Research Foundation	00002981	00002640
Harvard University (School of Public Health)	**00002642**	00000271

Table B: Education Compliance for Investigators

Name	Institution	Protection of Human Subjects Education Program
Dorairaj Prabhakaran	PHFI	CITI*
Ranjani Harish	MDRF	CITI
Viswanathan Mohan	MDRF	CITI
Jeemon Pinnayammakal	PHFI	CITI
K.M. Venkat Narayan	Emory	CITI
Mary Beth Weber	Emory	CITI
Mohammed K. Ali	Emory	CITI
Monique Hennink	Emory	CITI
Donna Spiegelman	Harvard	CITI

Name	Institution	Protection of Human Subjects Education Program
Walter Willett	Harvard	CITI

**Collaborative Institutional Training Initiative (CITI)* is a web-based training program in human research subjects protections recommended by NIH*

c. Protection of Vulnerable Populations

The study will not include pregnant women, fetuses, neonates, prisoners, or children.

3. Potential Benefits of the Proposed Research to Human Subjects and Others

All individuals at the worksites will benefit from participating in screening as it will provide them important health information about their weight and risk for developing diabetes and prediabetes. In addition, worksite environment changes will potentially benefit all employees by providing them with health information, access to healthy foods, and opportunities for exercise. Participants in the interviews and focus group discussions will be given the opportunity to share their views on health, worksite wellness, and the program. Intervention class participants will learn about lifestyle improvement and disease prevention and will potentially improve their cardiometabolic profile and prevent diabetes and/or diabetes-related complications. Training of peer educators and study participants on these topics will help to sustain and disseminate this knowledge into the community.

The trial will provide important information about individual views on diabetes and obesity, worksite-based lifestyle programs, worksite environment change, diabetes and cardiovascular risk factor prevention, and translation of lifestyle interventions, all in the context of India, a country with a large and growing burden of cardiometabolic diseases. Lessons from this trial can inform the development of worksite-based lifestyle programs in India and beyond.

4. Importance of the Knowledge to be Gained

The research study aims to fill deficiencies in knowledge regarding translation and delivery of a lifestyle improvement program at worksites in India and may have relevance for other countries, including the United States. The study will collect data on the cost and worksite impact of such a program, views on diabetes and obesity, impact of the program, acceptability to users and companies, and fidelity to such a program in India, filling gaps in the available literature. Outcomes of the study will be used to make recommendations for similar programs, with a focus on keeping such interventions low-cost, sustainable, easy to disseminate, and acceptable and helpful for employees and worksites.

5. Data and Safety Monitoring Plan

All study staff at each participating site will complete training in the protection of human subjects, including training in data handling and confidentiality. The project managers will administer all transfers, organization, storage, and back-up of study data. They will work closely with participating clinic investigators to ensure all data is secured and any edits can be tracked using password-protected access, automated edit tracking, audit trails, validation tools for data-entry (split screen views), and encrypted transfer facilities. To further protect employee participants, a Data Safety Officer will be identified for the study (this individual will not be affiliated with the project); this person will visit worksites annually and ensure proper data handling and complete separation of study data and worksite-based databases (e.g., databases of health information collected at the employee health center).

Adverse events at study sites will be reported by the site coordinator to the study coordinating center, which will inform the study PIs, the site health officer, and ethics committees at the collaborating institutions. Serious adverse events (e.g., CVD events or death) that occur during the intervention or present during study testing will be brought to the attention of the study PIs and the health officer at the site. Participants will be referred to emergency care if necessary. In the event of

significant risks to human subjects or decreased likelihood of study completion, provisions will be made to consider premature discontinuation of the trial where deemed necessary or as recommended by external review boards (IRBs) or by consensus of the investigator group.