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Diabetes prevention in the Caribbean using Lifestyle Intervention and Metformin Escalation (LIME): Protocol for a hybrid Type-1 effectiveness-implementation trial using a quasi-experimental study design

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ABSTRACT

Background: Globally, several diabetes prevention interventions have been shown to be cost-effective, yet they have had limited adaptation, implementation, and evaluation in the Caribbean and among Caribbean-descent individuals, where the burden of type 2 diabetes is high. We report on the protocol for the Lifestyle Intervention with Metformin Escalation (LIME) study – an evidence-based diabetes prevention intervention to reduce the incidence of diabetes among Caribbean-descent individuals with prediabetes.

Methods: LIME is a hybrid type-I effectiveness-implementation quasi-experimental study taking place in 4 clinical sites in Barbados, Trinidad, the U.S. Virgin Islands, and Puerto Rico. LIME targets individuals who self-identify as Caribbean or Caribbean-descent and have high-risk prediabetes with a hemoglobin A1c (HbA1c) between 6 and 6.4%. Eligible participants in the intervention arm are enrolled in a six-week lifestyle modification workshop. Six months later, individuals who have not lost at least 5% of their bodyweight or continue to have an HbA1c of 6% or higher are prescribed metformin medication. In total, participants are followed for one year. The primary effectiveness outcome is proportion of individuals who lower their HbA1c below 6%.

Discussion: LIME is a unique diabetes prevention intervention for Caribbean and Caribbean-descent individuals. LIME utilizes a tailored lifestyle change curriculum, incorporates appropriate metformin prescribing when lifestyle change alone is insufficient, targets the highest-risk individuals with prediabetes, and is based in a clinical setting to ensure sustainability.

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1. Introduction

The North American and Caribbean region has the highest age-adjusted prevalence of diabetes in the world at 10.8% [1], with some countries in the Caribbean reporting prevalence rates of 18% [2]. This is significantly higher than both the worldwide prevalence and the prevalence in South and Central America, which is about 7.5% [1,3]. This high prevalence results in high diabetes-associated mortality: diabetes accounts for 13.8% of adult deaths in the Caribbean [3].

With such a high burden of disease and disease-associated mortality, diabetes type 2 prevention in this region is imperative. Since 2002, a number of studies globally have shown that diabetes prevention is effective and cost-effective. This prevention has taken the form of lifestyle modification that leads to 5–7% weight loss or use of metformin medication [4–9]. Despite these promising results and a continued rise in diabetes prevalence in the Caribbean, there have been very few diabetes prevention initiatives in the region [1,10]. We sought to address this gap in evidence-based diabetes prevention interventions for Caribbean populations.

We used a systematic approach to adapt and implement an evidence-based diabetes prevention intervention to the Caribbean. The Lifestyle Intervention with Metformin Escalation (LIME) combines lifestyle modification and appropriate metformin prescribing to reduce the incidence of type 2 diabetes. The objective of LIME is to test the hypothesis that a tailored lifestyle modification program for Caribbean-descent populations combined with guideline compliant medication prescribing of metformin will reduce hemoglobin A1c in high-risk individuals with prediabetes. This paper presents the rationale for the LIME intervention and the protocol for intervention. We adhere to the SPIRIT reporting guidelines for reporting clinical trials [11]. We anticipate that this paper will help inform other type 2 diabetes prevention interventions in the region.

2. Methods/Design

2.1. Study rationale

2.1.1. Current US-based guidelines for diabetes prevention

The American Diabetes Association (ADA) guidelines specify that lifestyle modification should be the first recommended treatment for individuals with prediabetes [12]. The guidelines then note that “metformin therapy for prevention of Type 2 diabetes should be considered in those with prediabetes, especially for those with BMI 35 kg/m², those aged 60 years or die between 6% and 6.4%. These individuals have the highest risk of developing diabetes in the next 5 years [20,21]. This is also the HbA1c range where diabetes prevention has been shown to be the most cost-effective [22]. Additional eligibility criteria are outlined in Table 1. The age range of participants is 40–60 years of age. Beginning enrollment at age 40 workshop leaders (some high-school education and English or Spanish literacy required).

2.1.3. Escalation to metformin medication

Participants who do not lose at least 5% of their bodyweight or reduce their HbA1c below the high-risk value of 6% within 6 months of the workshops beginning are prescribed metformin medication per ADA recommendations.

2.2. Study objectives

We hypothesize that LIME, as a tailored intervention to a Caribbean population, will lead to a significant reduction in hemoglobin A1c in individuals with prediabetes.

The objectives of the LIME trial are:

1. Primary Objective: to determine the effectiveness of a tailored lifestyle modification workshop series combined with metformin medication, when needed, to reduce hemoglobin A1c in individuals with high-risk prediabetes.
2. Secondary Objective: to determine key implementation outcomes that influence the effectiveness of the LIME trial.

2.3. The LIME trial

2.3.1. Study design

LIME is a hybrid type-I effectiveness-implementation trial where the primary outcome is effectiveness and the secondary outcome is implementation [17]. We power the study for clinical effectiveness to reduce HbA1c, a primary diabetes outcome. At the same time, understanding the barriers and facilitators of implementation is critical to overcome prior challenges to the adoption and sustainability of diabetes prevention interventions [18,19].

LIME utilizes a quasi-experimental study design. It is a pre-post study design with a non-equivalent control group. LIME clinical sites are intervention sites; control participants are selected using frequency matching (based on age, sex, and BMI class) from an ongoing cohort study in each island site.

LIME was approved by the Yale University Human Investigation Committee (HIC) and the Institutional Review Boards of the University of the West Indies and the University of Puerto Rico Medical Sciences Campus. USVI and Trinidad site investigators were included in the Yale HIC Protocol. Informed consent was required for participation in the study.

2.3.2. LIME intervention sites

The LIME intervention is being conducted in four clinical sites in Barbados (St. Michael), Puerto Rico (Carolina), Trinidad (South West Region), and the US Virgin Islands (St. Thomas). These are the four islands that the Yale School of Medicine has historically worked closely with through the Eastern Caribbean Health Outcomes Research Network (ECHORN). A total of 30 eligible organizations on the four islands received email notifications about the LIME project and were encouraged to apply to serve as a clinical site for the study. We received four applications (one from each island), and all were chosen to participate. All four are public clinics that are either affiliated with the island’s Ministry of Department of Health or is a federally qualified health center.

2.3.3. Intervention participant eligibility

In LIME, we targeted patients with a hemoglobin A1c (HbA1c) between 6% and 6.4%. These individuals have the highest risk of developing diabetes in the next 5 years [20,21]. This is also the HbA1c range where diabetes prevention has been shown to be the most cost-effective [22]. Additional eligibility criteria are outlined in Table 1. The age range of participants is 40–60 years of age. Beginning enrollment at age 40 workshop leaders (some high-school education and English or Spanish literacy required).
allowed us to use frequency-matched controls from an ongoing cohort study conducted on the four islands. The upper end of the age cutoff was set at 60 because current ADA guidelines do not recommend use of metformin medication for adults above the age of 60. The BMI cutoff of 60 allows more flexibility, given the large population of Asians in Trinidad and evidence that many individuals with high cardiovascular risk are missed by BMI alone [23]. Individuals with gestational diabetes have a lower threshold for metformin initiation per ADA guidelines and were therefore excluded. Individuals also needed to have insurance to cover metformin medication and basic laboratory testing.

2.3.4. Intervention participant recruitment (completed portion of the study)

Recruitment of participants occurred primarily in the clinics. Study flyers were displayed across the clinics to advertise the study. Providers were sensitized to the study and encouraged to refer potentially eligible patients even if there was no prior HbA1c test. Potentially eligible participants were identified by provider referral or self-referral. Participants were also recruited at community outreach events hosted by the respective clinical sites. If participants met all criteria but did not have an HbA1c test result on file in the last 30 days, they received a point-of-care HbA1c test. If the test result was between 6% and 6.4%, participants were enrolled (through completion of a survey, clinical assessment, and lab tests) and scheduled to attend one of the upcoming workshops. All participants were consented prior to receiving an HbA1c test. Recruitment and enrollment of participants across all sites has been completed.

2.3.5. Control participants

Control participants come from the Eastern Caribbean Health Outcomes Research Network (ECHORN) Cohort Study (ECS) [24]. Initiated in 2013, the ECS is an ongoing study of approximately 3000 adults aged 40 and above on the islands of Puerto Rico, the US Virgin Islands, Trinidad, and Barbados. ECS participants returning for their Wave 2 follow up, starting in January 2018, were considered as potential control participants. During this visit, participants completed both a survey and a clinical assessment (the same as the LIME study assessments). Participants are frequency matched by island, age group (40–50, 51–60 years of age), sex, and BMI class. All control participants are required to have an HbA1c between 6% and 6.4%. These baseline characteristics of ECS participants who serve as a control population are obtained from the online cohort study data. Eligible participants are then contacted to consent to participation in the study as a control. If they consent, they are asked to return to the ECS clinical assessment site 12 months after the baseline values were obtained to gather follow up survey, laboratory, and clinical assessment endpoints. Control participants are recruited from the ECS rather than from the intervention sites to reduce contamination; while we prioritize comparability between the intervention and control participants, this results in a non-equivalent control group. Given similar sociodemographics in the areas of the island where LIME is taking place and where the ECS participants reside, we believe the control population to be comparable to the intervention participants. Control participant recruitment is ongoing.

2.4. LIME intervention

The LIME intervention consists of two main components: exposure to lifestyle modification workshops and escalation to metformin medication when needed. Fig. 1 provides a schematic overview of the trial. Fig. 2 covers the SPIRIT recommendations for enrolment period, intervention, and follow up.

2.4.1. Participant engagement in LIME workshops (completed portion of the study)

Eligible intervention participants signed up for an upcoming LIME workshop session based on most convenient timing. All clinical sites offered at least 2 workshops and provided options for different times of the day. Workshops were held at the clinical sites. Eligible participants who completed a baseline assessment had to attend at least one workshop session before being considered enrolled in the study. Workshops were led by trained clinic staff and affiliates. Each implementing site had to identify staff members who were interested and able to attend the training session. Training sessions were 4 full days, delivered by master trainers who were subsidized by the project. Workshop leaders were not paid for or subsidized by the project; this was considered part of their role in the clinic.

Workshops were each 2.5 h long and occurred weekly for 6 sessions, for a total of 15 h. There were two workshop leaders per workshop session. Each workshop group created a WhatsApp group to allow members to communicate with each other throughout and beyond the 6-week session. This WhatsApp group was also used to send monthly reminders about skills and tools learned during the workshop series. Workshop participants were also given access to the iHEEDapp™, which is free and was customized for each island site to list local healthy lifestyle resources (e.g. farmers market, gym, walking groups, health fairs).

Participants were called by their workshop leader 3 months after the
start of the workshops to remind them of the LIME study and discuss the extent to which they are continuing lifestyle changes. Any questions the participants might have about lifestyle change can also be discussed.

All sites have completed their workshop sessions and the 3 months follow up calls.

2.4.2. Metformin escalation (ongoing part of the study)

Six months from the start of their workshop session, participants are called back for a follow up visit. In addition to obtaining the follow up measurements mentioned previously, this visit is used to determine which participants will need to be prescribed metformin. Participants who lose at least 5% of their bodyweight or bring their HbA1c below 6% do not require metformin escalation. These participants are asked to continue their lifestyle modifications. The remaining participants are prescribed metformin medication, consistent with the 2017 ADA guidelines that recommend metformin therapy if lifestyle change alone is not enough. The dose of metformin to be used in diabetes prevention is not elucidated in the guidelines. The DPP used a high dose of 850 mg twice a day; limited data about the effectiveness of lower doses of metformin for diabetes prevention among minority patients in the US is available [8,12]. Therefore, we start with a dose of 500 mg of metformin twice a day at 6 months. Part of the rationale for this is to see if a lower dose of metformin can be effective given its significant side effect profile (mainly diarrhea) when started at 850 mg. Participants who have significant side effects to metformin can discuss symptoms with a nurse via phone; dose reduction is attempted first using 500 mg daily and then gradually increasing to twice a day. If still not tolerated, metformin is discontinued. This discontinuation is recorded in REDCap by the RA during the follow up call. It is also documented when the participant returns for their 12-month follow up visit and is asked about their adherence to Metformin. Metformin adherence is documented at the 12-month visit via self-report and pill count when available. After the follow up visit, a 3-month check-in by phone reminds participants of the lifestyle modifications and, when appropriate, enquires about metformin medication adherence. Monthly WhatsApp messages with tips from the workshops are continued until the 12-month follow up.

2.4.3. Participant retention (ongoing part of the study)

We promote participant retention through the 3-month follow up phone calls, which allow us to “check-in” and answer any study-related questions that they have.

2.4.4. Study outcomes

As a hybrid effectiveness-implementation study, we prioritize effectiveness but also assess implementation. The primary effectiveness outcome for this study is change in HbA1c. Secondary outcomes include changes in weight, other anthropometric measures of obesity (waist circumference, waist-to-hip ratio, BMI), cholesterol, blood pressure, diabetes self-efficacy score, and quality of life. For the second objective focused on implementation, the outcomes of interest include reach, adoption (individual/institutional), fidelity (to both the protocol and the workshop curriculum), acceptability, appropriateness, cost, and sustainability. The evaluation plan below lists further details.

2.4.5. Sample size

Our target enrollment is 120 in the intervention arm and 120 in the control arm. This will allow us to detect a 20% difference between the intervention and control arms in the proportion of individuals whose HbA1c falls below 6% over a 12-month period, with 80% power and a two-sided alpha of 0.05. In addition, it allows for a 30% loss to follow up. This loss to follow up was intentionally conservative and based on prior work with the original intervention done in New York City [15]. This sample size also powers us to detect a change in average HbA1c of 0.2, which was the observed difference in HbA1c between the lifestyle change arm and placebo arm in the DPP [14]. In addition, we are powered to observe a change in the average weight, of at least 5%, before and after the intervention.

2.4.6. Study timeline and duration

The study duration is 12 months, as this is the timeframe over which we would expect to see differential change in HbA1c between the intervention and control arms. Intervention participants have study visits at baseline, 6 months after the start of the workshop, and 12 months after the start of the workshop. Control participants are seen at baseline and at 12 months.

2.5. Data collection and management

Study data include a survey, clinical assessment, and laboratory studies. Survey domains include sociodemographic measures, family history, past medical history, self-efficacy, Global Physical Activity Questionnaire [25], Dietary Screening Questionnaire [26], PROMIS Global Health for Quality of Life [27], and Social Desirability Scale [28]. Metformin adherence is assessed via self-report and pill count. Clinical assessment includes standardized measurement of blood pressure, height, weight, and neck, waist, and hip circumferences. Laboratory studies include HbA1c, cholesterol, and creatinine. Creatinine is checked only once as a criterion for eligibility if not obtained in the last year. Cholesterol is a serum test sent to the clinic lab; cholesterol is checked only once as a criterion for eligibility if not obtained in the last year. Cholesterol is a serum test sent to the clinic lab; cholesterol is checked at baseline and at 12 months. HbA1c is assessed using the point-of-care A1cNow® device (PTS Diagnostics, Whitestown, IN). HbA1c testing is not readily available in clinic laboratories, with frequent reagent shortages disrupting continuous testing. Point-of-care devices allow us to ensure testing can be carried out and real-time decisions can be made on eligibility of the participant for the study.

Study personnel attended virtual training sessions on conducting portions of the clinical assessment to ensure consistency. They also attended virtual training on use of the A1cNow® machine. These trainings have all been completed.

All data are collected on the REDCap data collection system and backed up onto a secure server. Quality and completeness of data are checked weekly by the coordinating center at the Yale School of Medicine. Any discrepancies or missing data are communicated to the sites in real-time. Missing data on surveys are obtained by contacting the participant, missing laboratory values are addressed by asking participants to go to the laboratory for testing cholesterol and/or creatinine, missing clinical assessment values could not be filled and will need to be handled analytically.
2.6. Evaluation plan (ongoing part of the study)

We are conducting a concurrent mixed methods evaluation using the RE-AIM (Reach, Effectiveness, Adoption, Implementation, Maintenance) framework [29,30]. Table 2 outlines how we define each RE-AIM domain and the data sources for the evaluation. Data are being collected prospectively to ensure that we capture necessary survey, clinical assessment, laboratory, and programmatic information to assess RE-AIM domains.

2.6.1. Quantitative analysis plan (forthcoming part of the study)

We will use the chi-squared test to compare the proportion of individuals who reduce their HbA1c below 6% over the 12-month period in the intervention and control groups as the primary outcome. Differences between the intervention and control groups in the secondary outcomes of average change in HbA1c, weight, BMI, systolic blood pressure, cholesterol, self-efficacy score, and quality of life will be compared using Student’s t-tests. Within the intervention arm, we will use chi-squared and t-tests to identify any patient-related factors that are associated with the primary outcome of HbA1c reduction below 6%. We will also compare outcomes among sites using chi-squared tests and analysis of variance (ANOVA), as appropriate.

2.6.2. Qualitative analysis plan (ongoing part of the study)

Qualitative interviews are conducted with both implementers and participants by trained research assistants on each island site. Interviews take place 6 months into implementation. Implementers are purposefully sampled to include personnel who are highly engaged and those who are less so, personnel with different roles in the project, and administrators. We are interviewing approximately 4 implementers per site (total of 16) with more interviews as needed to reach thematic saturation. Participants are purposefully sampled to include men and women, those with high and low workshop attendance rates, and those on and not on metformin. We plan to interview individuals who were eligible but did not participate (future work). We are interviewing approximately 4 participants per site (total of 16) with more interviews as needed to reach thematic saturation. Interviews will be transcribed and translated when appropriate. Thematic content analysis is being used to analyze transcripts. Dedoose® (SocioCultural Research Consultants, LLC, California) software is used to facilitate data analysis.

2.6.3. Ethics

The protocol, site-specific informed consent forms, participant recruitment and education materials, surveys, and follow-up call scripts are all approved by the Yale University Human Investigation Committee (HIC). In addition, approval was sought from the respective IRB at the University of the West Indies and the University of Puerto Rico. USVI and Trinidad are covered by the Yale HIC. The protocol presented here is the third version of the protocol approved by the Ethics Review Boards. Written consent for the participation in the project was obtained in person by trained research staff at each site. All consent forms and participant materials were translated into Spanish for the Puerto Rico site. Separate consent forms were used for control participants. Any and all protocol deviations are reported to the Yale HIC.

All study-related information is stored on the online secure REDCap data collection system. Research staff at each site can only access data for participants at their site. Access is password protected and data are backed up in a secure Yale server. The paper consent forms use participant’s unique ID number and are stored securely in a locked file cabinet at each site. The data coordinating center at Yale has access to all site data and regularly monitors data quality. All site investigators will be given access to the final de-identified data sets following data collection.

Table 2

| RE-AIM Domain                                           | Data Source                                                                 |
|---------------------------------------------------------|------------------------------------------------------------------------------|
| Reach: absolute number and characteristics of those participating in the program | Programmatic data                                                            |
| % of eligible patients with prediabetes who participate in at least one workshop session Barriers and facilitators to reach | Qualitative interviews                                                        |
| Effectiveness: program effectiveness as defined by primary and secondary outcomes |                                                                            |
| Primary outcome: change in HbA1c                        | POC/serum results                                                           |
| Secondary outcomes: BMI, blood pressure, cholesterol, self-efficacy, diet, physical activity | Clinical assessment, laboratory, survey                                       |
| Percentage of participants enrolled at end of study period | Programmatic data                                                           |
| Lifestyle modification workshop attendance              | Programmatic data                                                           |
| Percentage of participants placed on Metformin           | Pill count                                                                  |
| Metformin adherence                                      | Survey                                                                      |
| Choice of sustainability approach to maintain lifestyle change | Programmatic data                        |
| Use of the iHEEDApp                                      | Programmatic data                                                           |
| Use of WhatsApp                                         | Programmatic data                                                           |
| Barriers and Facilitators to: lifestyle modification, sustaining lifestyle change, medication adherence, workshop attendance | Qualitative interviews                                                        |
| Adoption: adoption of the program at the clinic and individual level |                                                                            |
| % of eligible clinic sites who applied to participate    | Programmatic data                                                           |
| % of staff at each site who were trained                 | Qualitative interviews                                                      |
| % of trained staff who participate in teaching workshops Barriers and facilitators to adoption |                                                                            |
| Implementation: Key features of program delivery         |                                                                            |
| Protocol adaptations at each site                        | Descriptive                                                                 |
| Fidelity to the protocol                                | Programmatic data                                                           |
| Fidelity to workshop curriculum                         | Workshop fidelity assessment                                                |
| Cost-effectiveness                                      | Programmatic data                                                           |
| Barriers and Facilitators to implementation (acceptability, appropriateness, feasibility also assessed) | Qualitative interviews                                                        |
| Maintenance: extent to which clinics sustain the program |                                                                            |
| % of clinics that institutionalize the intervention      | Future work                                                                 |
| Sustainability of LIME at each site long-term           | Qualitative Interviews                                                      |
and cleaning. The Yale Human Subjects Investigation Committee serves as the Data Monitoring group that regularly monitors any reported events from execution of the protocol.

2.6.4. Dissemination plan

Project progress and any interim analyses are shared at quarterly meetings of the consortium implementation work group (key stakeholders). An end-of-study report will be shared with stakeholders, implementing sites, and participants. In addition, results will be presented at national conferences and submitted to peer-reviewed journals.

3. Discussion

The LIME trial was designed to assess the effectiveness and implementation of a tailored lifestyle modification workshop series and appropriate metformin medication prescribing in reducing the incidence of diabetes among individuals of Caribbean descent with high-risk prediabetes. While there have been many diabetes prevention trials in the past, the LIME trial is innovative in the following ways: it presents a lifestyle workshop series that is tailored to Caribbean and Caribbean-descent populations, it is clinic-based (ensuring the sustainability of the program), it integrates guidelines to add metformin therapy if lifestyle change alone is insufficient, and it assesses the impact of the intervention in individuals with the highest risk of developing diabetes in the next 5 years. If study effectiveness is determined, this study will facilitate future dissemination of the intervention to other Caribbean island states, to Caribbean communities in the US, and to other parts of the world.

There are a few limitations of this study that we should note. The use of point-of-care testing is not yet approved for the diagnosis of diabetes or prediabetes. However, its use in low-income settings makes it more practical given both intermittent access to reagents for standard, laboratory-based testing and the need for more timely test results to prevent delays in diagnosis, treatment, and follow up. These needs outweigh concerns over somewhat lower test accuracy. In addition, to increase test utility, we use HbA1c ranges (6–6.4% and less than 6%) rather than absolute values. Furthermore, there have been reports of inaccuracy of HbA1c for the diagnosis of diabetes in Caribbean populations [31], with the suggestion that it is not always compatible to fasting glucose in classifying individuals as having diabetes. Given we are targeting a high-risk group of individuals with prediabetes (HbA1c 6–6.4%), this is unlikely to be an issue, since we are still capturing individuals with prediabetes. We use the same modality to check blood sugar control at follow up (and in controls); therefore, the comparison of values before and after the intervention remains valid.

Despite these limitations, this intervention is promising. LIME introduces a practical approach of integrating diabetes prevention initiatives into existing primary care clinics to reduce the incidence of diabetes among the highest-risk individuals with prediabetes in the Caribbean.

3.1. Trial status

The LIME trial has completed recruitment and enrolment of participants in the intervention arm. Furthermore, the workshops in each island site has been completed. Follow up of participants is ongoing. Evaluation of the intervention is ongoing. This is the third protocol version of the LIME trial. Recruitment started in the summer of 2018.

Ethics approval and consent to participate

LIME was approved by the Yale University Human Investigation Committee and the Institutional Review Boards of the University of the West Indies and the University of Puerto Rico Medical Sciences Campus. Informed consent was required for participation in the study.

Availability of data and materials

Data is not available at this time as trial is still recruiting.

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Authors’ contributions

SH, MNS, OPA, MD, CH, SW conceptualized the study and contributed to the protocol. AC provided implementation science consultation on the project. EL facilitated the stakeholder engagement meetings. LF, JPC, JH, NS, EG implemented LIME in the island sites. GA served as the T-Trainer expert. SH wrote the first draft of the manuscript. All authors reviewed and edited the manuscript.

Declaration of competing interest

The authors declare that they have no competing interests.

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List of Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| CDSMP        | Chronic Disease Self-Management Program |
| DPP          | Diabetes Prevention Program |
| DSMP         | Diabetes Self-Management Program |
| EHPDP        | East Harlem Partnership for Diabetes Prevention |
| HbA1c        | Hemoglobin A1c |
| HEED         | Help Educate to Eliminate Diabetes |
| LIME         | Lifestyle Intervention with Metformin Escalation |
| NDPP         | National Diabetes Prevention Program |
| USVI         | US Virgin Islands |

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.conctc.2021.100750.

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