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Design of a cluster-randomized trial of the effectiveness and cost-effectiveness of metformin on prevention of type 2 diabetes among prediabetic Mexican adults (the PRuDENTE Initiative of Mexico City)

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Abstract

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Introduction—Type 2 diabetes (T2D) is a global epidemic, and nations are struggling to implement effective healthcare strategies to reduce the burden. While efficacy studies demonstrate that metformin can reduce incident T2D by half among younger, obese adults with prediabetes, its real-world effectiveness are understudied, and its use for T2D prevention in primary care is low. We describe the design of a pragmatic trial to evaluate the incremental effectiveness of metformin, as an adjunct to a simple lifestyle counseling.

Methods—The "Prevención de la Diabetes con Ejercicio, Nutrición y Tratamiento" [Diabetes Prevention with Exercise, Nutrition and Treatment; PRuDENTE, (Spanish acronym)] is a cluster-randomized trial in Mexico City's public primary healthcare system. The study randomly assigns 51 clinics to deliver one of two interventions for 36 months: 1) lifestyle only; 2) lifestyle plus metformin, to 3060 patients ages 30-65 with impaired fasting glucose and obesity. The primary endpoint is incident T2D (fasting glucose ≥ 126mg/dL, or HbA1c ≥ 6.5%). We will also measure a range of implementation-related process outcomes at the clinic-, clinician- and patient-levels to inform interpretations of effectiveness and enable efforts to refine, adapt, adopt and disseminate the model. We will also estimate the cost-effectiveness of metformin as an adjunct to lifestyle counseling in Mexico.

Discussion—Findings from this pragmatic trial will generate new translational knowledge in Mexico and beyond, both with respect to metformin's real-world effectiveness among an 'at-risk' population, and uncovering facilitators and barriers to the reach, adoption and implementation of metformin preventive therapy in public primary care settings.

1. INTRODUCTION

Type 2 diabetes (T2D) is a global epidemic; more than one in eleven adults have T2D, and one in ten are projected to have it by 2040 [1]. Among the Organization for Economic Cooperation and Development members, the United States (US) and Mexico are first and second in prevalence of T2D [2]. Due to social, economic, environmental and genetic factors, people of Mexican origin are particularly susceptible to T2D and its complications [3]. In Mexico, T2D and prediabetes prevalence are 14% and 33.5%, respectively [4,5]. In the US, Mexican American adults are an ethnic group with one of the highest prevalence of T2D (23.8%) and prediabetes (38%) [6]. Mexico recently declared T2D as a national emergency, as it is a leading killer in adults. There is an urgent need to implement scalable interventions to prevent, control and reduce the burden of T2D in this population, particularly in primary care settings.

Efficacy studies[7] demonstrate that, for prediabetes, intensive lifestyle interventions and metformin can reduce incident T2D (by ~50% and 30%, respectively); for younger, obese individuals, however, metformin is especially effective (~50%)[7]. While Diabetes Prevention Program (DPP)-like lifestyle interventions have been translated in a number of community effectiveness studies [8], the reach has been low [9], and no large studies involve Hispanic, or low-income populations, for whom lifestyle changes are challenging [8]. Real-

world effects of metformin are understudied, and the use of metformin for T2D prevention in primary care is low [10,11]. Likewise, determining the added effect of metformin, when used as an adjunct to lifestyle counseling, has been the subject of few studies, hampered by low metformin doses[12] or their lack of inclusion of Hispanic populations [13]. We have identified only three published controlled studies of DPP-like interventions targeting Hispanic populations in the US, each hampered by small sample sizes, short follow-up, neither implemented interventions in primary care, and only one featured a design that could assess the effect of metformin [14–16]. Finally, while metformin has been deemed cost-effective based on efficacy studies, no research has examined whether implementation of metformin in primary care would prove to be cost-effective – a question of utmost public health and policy importance [8,11].

As a result of a bi-national, interdisciplinary collaboration between the University of California and Mexico's largest research institutions [17,18], we have leveraged an unprecedented opportunity to study the real-world implementation and impacts of a T2D prevention initiative in Mexico City's Ministry of Health (MxCMoH) - one of the largest municipal health systems in the world: the "Prevención de la Diabetes con Ejercicio, Nutrición y Tratamiento" [Diabetes Prevention with Exercise, Nutrition and Treatment; PRuDENTE (Spanish acronym)]. Mexico has a national healthcare system with primary care centers similar to those in the US safety net. Because Mexican Americans receive most of their care in public clinics, findings from this trial will generate new translational knowledge to inform health policy in Mexico, and will also yield novel insights critical to advancing primary care-based T2D prevention for Mexican Americans in US public delivery systems, and vulnerable populations globally.

2. METHODS

2.1 Aims and objectives

This study aims to 1) determine the incremental effectiveness of metformin, used as an adjunct to a simple lifestyle counseling, to prevent T2D in a low-income Mexican population with prediabetes receiving care in a public system in Mexico City; 2) examine a range of implementation process outcomes at the clinic-, clinician- and patient-levels to inform our interpretations of effectiveness and enable efforts to refine, adapt, adopt and disseminate the model; and 3) estimate the cost-effectiveness of metformin as an adjunct to lifestyle counseling in the Mexico context, and model cost-effectiveness for people of Mexican origin in the US.

2.2 Establishing the partnership with Mexico City's Ministry of Health

A Memorandum of Understanding (MOU) was signed in May 16, 2017 by the University of California, San Francisco (UCSF) and the Secretary of Health of Mexico City to conduct this clinical trial. The purpose of the MOU was to formalize a partnership among academic institutions in Mexico and the US with the local health authorities in Mexico City. The two Mexican academic institutions are part of the National Institutes of Health of Mexico, with ample trajectory in T2D research and training: The National Institute of Public Health (INSP, by its Spanish acronym) and the Salvador Zubiran National Institute of Medical

Sciences and Nutrition (INCMNSZ, by its Spanish acronym). From UCSF, two academic units were involved: The Institute for Global Health Sciences, and the Center for Vulnerable Populations. The US and Mexican academic centers were responsible for the design of the trial, while the Secretary of Health offered to provide the clinical settings, operational support and supplies for the study.

2.3 Study setting

Mexico has a decentralized health system, with 32 federal states responsible for health care delivery to their populations. Mexico City, a federal state, has a population of about 9 million, and almost 22 million when taking into account the total metropolitan area. While 60% of Mexico City residents are covered by health insurance through private or public sector employees, much of the low-income population receives coverage through *Seguro Popular*, a public form of universal basic healthcare [19]. These low-income populations receive health services through the MxCMoH. MxCMoH oversees a massive network of primary care and public hospitals, including 220 primary care centers [20], from which 51 geographically dispersed clinics were selected to participate in PRuDENTE (see randomization, below, and Figure 1). Every day, this network provides >21,000 outpatient visits and >2,000 emergency room (ER) visits, caring for ~2.3 million low-income people annually. The network has 11,000 physicians, >9,000 nurses, and 12,000 support staff. The annual budget is ~$1 billion US dollars [21].

2.4 Ethics and dissemination

The study protocol has been approved by the Committee on Human Research of the Mexico City Ministry of Health. Approval of data and biobank storage has been obtained from INSP, and INCMNSZ, respectively.

2.5 Study Design

The study design is a longitudinal cluster-randomized controlled trial with clinics as the unit of randomization. The study randomly assigns 51 clinics to deliver one of two interventions for 36 months for a total of 3,060 participants (60 per clinic): 1) lifestyle only (LSO) versus 2) lifestyle plus metformin, 850 mg twice daily (LS+M) (Figure 2). A cluster randomized design was selected for its feasibility within the set structure of the Mexico City Ministry of Health primary care centers; the intervention was more feasibly administered to all subjects chosen to participate within each clinic. This design also minimizes contamination across clinics.

2.6 Randomization

The MxCMoH has 220 primary care centers that represent "medical homes"; among these, 120 provide comprehensive primary care and full laboratory services. To create the PRuDENTE sample, 51 clinics were randomly sampled from this pool of 120 (Figure 1). In this pool, to improve generalizability and examine variation in clinic-level effects, the 120 clinics were first stratified and categorized according to population size based on number of patients ages 30–65 years who made >2 visits in the prior 12 months: small (<9K patients); medium (9–15K); and large (>15K). Within each population size stratum, 17 clinics were

then randomly selected and then randomly assigned to LSO vs. LS+M arms (25 to LSO and 26 to LS+M in total). Study participants, healthcare providers and investigators will not be blinded to randomization assignment for practical and safety reasons. However, evaluation of primary and secondary outcomes will be blinded.

2.7   Study Participants

The study involves 51 primary care clinics in Mexico City. Each clinic is issued an enrollment target of 60 participants, defined as those who meet eligibility criteria, agree to participate, and provide informed consent and baseline measurements. Each day, the clinic nurse identifies those who met eligibility criteria (see below) including: (1) are attending a routine clinic visit, (2) have impaired fasting glucose (100-125mg/dL), (3) have demonstrated 2 clinic visits in prior 12 months based on chart review, (4) are registered with *Seguro Popular*, (5) are ages 30-65 and (6) have a body mass index (BMI) 30kg/m^2. Exclusion criteria include having a prior diagnosis of T2D, already taking metformin, having an allergy to metformin, being pregnant, having a diagnosis of active alcoholism or substance abuse, renal insufficiency (prior diagnosis, oreGFR <30 mL/min/1.73 m2 or serum creatinine >2.0 mg/dL), hepatic insufficiency (previous diagnosis of cirrhosis or hepatic enzymes 3x normal [ALT >180 U/L, AST >126 or GGT >207 among men and >111 among women]) (Box 1).

2.8   Recruitment of Participants

Patients are recruited from the 51 PRuDENTE clinics. Eligible patients who agree to screening are asked to provide a fasting blood sample (no food or drink other than plain water for >8 hours). If they recently ate, patients are invited to return within 7 days to provide a sample. Tests at screening include fasting plasma glucose (FPG), renal panel, and liver function tests. Patients receive a follow-up appointment with the PRuDENTE nurse diabetes educator (NDE) within 7 days after blood draw to review results (normal, prediabetes, or diabetes range). Those whose screening reveals impaired fasting glucose (IFG), and are otherwise eligible, proceed to the enrollment phase (below). Those with FPG >125 mg/dL are excluded, informed of the possibility of their having T2D, and managed based on established clinic protocols. Patients whose FPG is <100 mg/dL are also excluded and are provided a brochure on diet and physical activity.

The NDE then invites eligible patients to participate in PRuDENTE. The NDE initiates an informed consent process describing (a) prediabetes and risk of progression; (b) goals of the project (prevent or delay T2D); (c) potential benefits of participation; (d) potential harms of participation (loss of confidentiality, time requirements, injuries related to physical activity, adverse effects of metformin); (e) the need to provide blood, urine and anthropometric measurements at baseline, 12, 24 and 36 months, and a questionnaire at baseline, 12, 24 and 36 months; (g) that participation is voluntary. Patients who consent are considered to be PRuDENTE participants and their status entered into the database; patients who do not participate also have their status entered, and are provided a T2D prevention brochure. All study-related information is collected by each clinic and is organized and stored in a secure, password-protected database, maintained at INSP.

2.9   Study visits and examinations

Clinic staff were first trained and directed by MxCMoH and the INSP Project Coordinator to initiate systematic screening of potentially eligible patients starting July, 2017. With 60 individuals targeted to be enrolled per clinic, the LSO arm will have 1500 and LS+M will have 1560 participants at baseline. Each clinic has designated a NDE and a primary care physician (PCP) to deliver interventions. In total, 102 clinicians (51 NDEs and 51 PCPs) are participating in PRuDENTE. All 51 NDEs and 51 PCPs have undergone two full-day training sessions conducted by INSP in spring of 2017 to optimize fidelity to survey procedures; ensure reliability of anthropometric measurements; ensure clarity regarding which blood and urine tests to obtain; and provide instruction and material for storing and transporting bio-samples. Any new NDEs or PCPs due to turnover of personnel undergo the same training prior to intervening in PRuDENTE. All NDEs and PCPs received a manual with the protocol and copies of the questionnaire, and practiced administering the questionnaire and anthropometric testing, and were certified by INSP staff.

2.9.1   PRuDENTE Questionnaires—PRuDENTE participants proceed to the baseline research assessment to be administered face-to-face by the trained NDE. All participants are asked to provide responses to baseline, 12, 24 and 36-month questionnaires, with the last to be obtained on the final clinic visit before the study ends (in the last month of exposure). The questionnaire employs measures validated in the US and Mexico (Table 1) on food frequency (FFQ), food insecurity and physical activity, as well as tobacco and alcohol use, personal past medical history, family history, medication use, lifestyle change self-efficacy, and quality of life. Twelve, 24 and 36-month questionnaires will repeat relevant assessments, and (for LS+M arm) will also ask participants to report metformin adherence.

2.9.2   Food Frequency Questionnaire—Dietary information is collected through a previously validated, semi-quantitative 130-item FFQ that has been used in the Mexican National Health and Nutrition Surveys [22,23]. The questionnaires specify how often, on average, they consumed a specified commonly used unit or portion size of the food or beverage over the previous week.

2.9.3   Food Insecurity—Household food insecurity (HFI) is measured with the well validated Latin American and Caribbean Food Security Scale (ELCSA, by its Spanish acronym) [24]. This food security scale includes 8 items that capture different levels of HFI severity in the three months prior to the survey administration. Each of the 8 questions is responded as yes, no, don't know or refused. We classify study participants in the following mutually exclusive categories based on the additive score of the eight adult ELCSA items and the recommended cut-off points: food-secure (score=0); mild HFI (1-3); moderate HFI (4-6); severe HFI (7-8) [24].

2.9.4   Physical Activity—Participants answer the Spanish version of the short-form International Physical Activity Questionnaire (IPAQ) to monitor changes in moderate-to-vigorous physical activity. Our team has previously evaluated the IPAQ against accelerometers in Mexican adults and found it to have sufficient reliability [25].

2.9.5   Anthropometric and biologic measures—At baseline, 12, 24 and 36 months, using standardized procedures, participants have their weight, height, and waist and hip circumferences measurements taken; arterial blood pressure (BP); and fasting blood, HbA1c and urine samples. All samples are kept on ice and transported daily to a central laboratory certified by the External Comparative Evaluation of Laboratories Program of the College of American Pathologists and stored in the new Metabolic Unit at INCMNSZ in Mexico City. Plasma and serum are separated and placed into 2cc cryogenic vials, stored at −80° C. Vials are bar coded linked to confidential patient ID numbers. Clinical chemistry parameters and lipid profile are measured using commercially available reagents (Synchron CX5 delta, Beckman Coulter, California, US). Insulin concentrations are measured using ELISA (AxSYM, Abbott). Urine microalbuminuria are measured using immunonephelometry (Beckman). In the LSO+M arm, to assess for adherence, 12- and 24-month samples will be analyzed for plasma metformin; a random sample of 10% of LSO participants will also be assayed to estimate contamination. Plasma metformin concentrations will be measured using HILIC-based analytical method (LaChrom 7000 series HPLC system, Merck-Hitachi, Darmstadt, Germany), shown to be accurate in detecting metformin at 10–2,000 ng/dL. Peak metformin levels are detected at 2.9 hours after ingestion of metformin, but reliably detect the presence of metformin up to 24 hours after ingestion [26]

2.10   Interventions

2.10.1   Lifestyle only arm—LSO clinics initiate the intervention within a week after baseline research assessments. LSO are delivered one on one by a NDE at baseline (1 counseling session of 45 minutes), and every 3 months thereafter, for a total of 36 months (up to 12 additional sessions of 15–20 min each). NDEs have been certified by MxCMoH to provide lifestyle counseling to T2D patients, including diet and physical activity. All PRuDENTE NDEs received 2 full-day trainings in spring 2017, using content developed and implemented previously by INSP, INCMNSZ and the University of California, San Francisco (UCSF). Components of this training are based on core curricular components from effectiveness studies of DPP and principles of motivational and patient-centered counseling sensitive to the health literacy of low income populations [27–29]. The primary objective of LSO is to promote weight loss over 3 years of ~5–7% [15]. The 6 core components of LSO are: (1) disclosing status of pre-diabetes and describing average risk of progression, with and without interventions, facilitated by a visual aid that uses icon arrays to overcome limitations in literacy and numeracy[30] and the teach-back method to ensure the information is understood [27]; (2) behavioral objectives related to diet, physical activity and weight loss, facilitated by 2 health educational brochures (for diet and for physical activity)[31,32] that utilize images, simple text, and a color-coded design; (3) assessment of current behaviors, using standardized, validated brief questionnaires (2 minutes each) and open-ended questioning; (4) elicitation of barriers and enablers of behaviors, complemented by open-ended questions, and facilitated by supportive statements; (5) provision of supportive feedback to remind participants of programmatic goals and review progress; (6) motivational techniques that incorporate participants' goals, barriers and facilitators to generate action plans; and (7) documenting in the database which of the 6 components were delivered and total time spent with the participant, using drop-down menus.

2.10.2 Lifestyle plus metformin arm—The LS component of LS+M is identical to LSO; the NDE delivers the simple lifestyle counseling and the metformin component is prescribed by the POP. LS+M includes provision of metformin, free of charge. Quality of metformin in MxCMoH is assured by the *Comisión Federal para la Protección contra Riesgos Sanitarios* (COFEPRIS, by its Spanish acronym) [33] using a rigorous process akin to the Food and Drug Administration (FDA) agency of the US. The metformin in Mexico is of high quality and bioequivalency [34] equal to the US. We use the metformin dose found efficacious in DPP (850mg twice a day) [7]. The metformin component is prescribed by PRuDENTE PCPs at baseline (1 counseling session of 20 min.), and every month thereafter at refill visits, for a total of 36 months (~10 min. sessions). Periodicity of visits was determined by MxCMoH; policy mandates medications be prescribed monthly to monitor adherence, effectiveness and adverse effects. All 24 participating PCPs in the metformin arm received 2 full-day trainings in spring 2017 using content previously implemented by INSP, INCMNSZ and UCSF [35]. The 9 components of LS+M: (1) disclosing prediabetes status; (2) describing metformin in a manner that resonates: an extract of an herbal remedy (French lilac) that prevents or delays T2D, with images of the flower, simple text to augment icon arrays, and instructions in use; (3) a discussion of adherence; (4) metformin side effects: gastrointestinal (GI) distress and diarrhea, vitamin B12 deficiency, and (very rarely) lactic acidosis; (5) a 30-day prescription of metformin (850mg), with dosing schedule of ½ pill before breakfast and dinner for 2 weeks (1st session only), followed by a full pill before breakfast and again before dinner (850mg twice a day), accompanied by a teach-back; (6) assessment of metformin adherence in the prior month, using a brief questionnaire and pill count that take ~2 minutes; (7) elicitation of barriers and facilitators to adherence; (8) provision of supportive feedback to remind participants of programmatic goals; (8) employing motivational techniques and generating an action plan; (9) refilling metformin; (9) ordering HbA1c and FPG every 6 months, and renal and liver panel every 12 months, to monitor therapy and safety; (10) documenting in PRuDENTE database, including components delivered.

2.11 Retention Protocol

MxCMoH will employ a robust set of strategies to retain participants and ensure adequate research follow-up. When/if a participant misses a PRuDENTE clinic (and/or research) visit, the clinic activates *Medicina a Distancia* – a centralized call center that maintains contact numbers and addresses – to encourage participants to attend visits and/or reschedule. Staff will attempt to reach patients on 3 occasions; if there is no response, a letter will be sent requesting the patient make an appointment with the clinician with whom they were scheduled. If a participant misses 2 consecutive visits, the clinic will then activate the *"Médico en Tu Casa'*program, in which a team consisting of a medical student and a nurse visit participants' homes to encourage them to attend visits and reschedule at a convenient time. These strategies have yielded high rates of patient engagement in ongoing routine chronic disease care in the MxCMoH, with annual retention of 92%.

2.12 Providing Feedback to Clinics

The PRuDENTE coordinator and quality monitors measure clinic performance for screening and treatment via the PRuDENTE database. Reports will be provided monthly to the

Medical Director of Primary Care for the first 6 months (on screening processes) and then quarterly (on retention and fidelity to intervention processes) and will display performance in relation to other clinics. The Medical Director will convey reports to clinics, and together develop plans to improve or maintain performance. These may include requests for technical assistance and re-training. All requests, and the amount of technical assistance provided by quality monitors, will be recorded in the PRuDENTE database. Finally, because of the importance of the 12, 24 and 36-month research visits, the PRuDENTE Project Coordinator will provide weekly feedback to each NDE regarding 12, 24 and 36-month visit attendance, and collaborate with the NDE to ensure additional retention plans for those who have failed to respond to outreach efforts. If all attempts to encourage the patient to return fail, the research staff at INSP will attempt to obtain the research interviews through *"Médico en Tu Casa",* or by phone, and encourage the patient to obtain the final anthropometric and biological measures through *"Médico en Tu Casa"* or the "*Unidad de Investigación de Enfermedades Metabólicas"* (Metabolic Unit) at INCMNSZ.

2.13 Reporting Adverse Events

The potential harm from the interventions is low but not insubstantial, and as part of the consent process, participants will be informed of these risks. The risks associated with changing one's diet relate to potentially higher costs for healthy foods. The risks associated with increasing physical activity relate to unintentional injuries and/or cardiovascular events in a previously asymptomatic patient. In general, lifestyle recommendations such as these represent the standard of care for people at risk of T2D, and clinicians routinely counsel patient of these risks. As such, we do not believe that the risks posed by participation in the lifestyle component will be significantly higher than the background risk for non-enrolled patients. However, we will implement a PRuDENTE reporting system for potential adverse events so as to continually assess these risks and intervene with respect to the study protocol if circumstances warrant. The risks associated with the metformin arm are also very low, but not insubstantial, and as part of the informed consent process, participants will be informed of these risks. The most common side effects of metformin are Gl distress and diarrhea, although these symptoms tend to be mild and are mitigated when the dose is slowly escalated, as we will do in PRuDENTE. Assessments for symptoms will be monitored monthly by PRuDENTE physicians. A smaller proportion of patients (~1-2%) may develop B12 deficiency after prolonged use; this is easily corrected with either B12 supplementation or removal of metformin. We will measure B12 levels at 36 months and inform the treating physician if their patient has developed B12 deficiency requiring action. Much rarer (<0.0001 %) events include lactic acidosis and death, but these are more likely to occur in patients with severe hepatic and renal insufficiency, both of which are exclusion criteria; in addition, PRuDENTE physicians will be monitoring renal and liver function every 12 months. While we have built several checks into the workflow and design of PRuDENTE to ensure close monitoring of participants (every 1-3 months), we have created an area on the web-based platform for PRuDENTE clinicians to report in real-time on the PRuDENTE clinical database whether they believe their patient may have experienced a potential adverse event. The PRuDENTE clinicians have been instructed as to the procedures for reporting such concerns both via the database, as well as through directly contacting the PRuDENTE project coordinator (a physician). In addition, any death of a PRuDENTE participant –

regardless of the suspected cause –must be reported. No matter how the information gets to her, the Coordinator will gather more detailed information from the clinician and then immediately present the event to the study Pis, both of whom are also physicians. The Pis will determine whether the case needs to be presented immediately to the Safety Monitoring Committee, or whether it can be adjudicated at a monthly committee meeting. The PRuDENTE Safety Monitoring Committee will log and adjudicate all reported events. All events suspected of being a result of PRuDENTE participation will be reported to the MxCMoH Committee on Human Research within 3 business days. The Safety Monitoring Committee will also advise the Pis to determine whether changes in protocol are deemed necessary, based on patterns of observed events, or whether the study should be terminated in the unlikely event that there are significant rates of serious adverse events.

2.14 Protocol for Participant Disenrollment or Early Termination/Closure

Disenrollment requests will be initiated by clinic staff via PRuDENTE database, and adjudicated, executed and documented by the PRuDENTE coordinator. These events lead to "disenrollment" from PRUDENTE interventions: (1) development of renal insufficiency, cirrhosis or hepatic enzyme elevations or pregnancy, via clinic monitoring; (2) participant reports to clinic that he/she is moving out of the clinic; (3) incident T2D. For these items, while no longer be exposed to PRuDENTE, these participants will be scheduled for 12, 24 and 36-month assessments. T2D ascertainment will rely on confirmatory testing at the INCMNSZ Metabolic Unit. Concern about incident T2D may arise from two sources: (1) the PRuDENTE study team, as part of its 12 and 24-month FPG and HbA1c values, and (2) the clinic, as part of its twice-annual monitoring of FPG and HbA1c. In the latter, clinic staff will be instructed that diagnosis of T2D requires confirmation before participant disclosure and initiation of new treatments. Within a week of receiving the abnormal results, the NDE will inform these participants that their routine tests revealed concern for T2D, and repeat tests will be requested. These repeat FPG tests will be obtained in clinic and transported to INCMNSZ, described above. If FPG or HbA1c again reveal T2D-range results, the NDE will be informed of confirmed T2D. The NDE will then consult with the clinic PCP to initiate a T2D-related treatment plan.

2.15 Outcomes

2.15.1   Primary endpoints—The primary outcome for PRuDENTE, comparing the LSO and LS+M arms, is incident T2D at 36 months, with additional time-points of 12 and 24 months to assess differential rates of progression. We define T2D as *either* a FPG   126 mg/dL at 36 months *or* a HbA1c value   6.5%, as determined by the INCMNSZ laboratory.

2.15.2   Secondary endpoints—Secondary outcomes include HbA1c as a continuous outcome. Because patients taking metformin may adhere less to other behavior changes, we will also measure: (a) weight, BMI and waist circumference, (b) physical activity, expressed as the average MET-hours/week, over 3 months, and (c) caloric intake and dietary quality over 1 week, from food-frequency questionnaires.

2.16 Sample size and planned statistical analyses

Analysis for aim 1 involves comparing the proportion at 36 months who have the dichotomous outcome of T2D between LSO vs. the LS+M, using the Chi-squared statistic. Because of the cluster-randomized clinical trial design, we account for within-clinic clustering using generalized estimating equation [36]. This analysis will be repeated for 12 and 24-month data. To estimate power, we used 2 models in which we varied 3-year incidence rates based on reasonable and evidence-based assumptions. While participants may have varying degrees of engagement with PRuDENTE, we pursue an intent-to-treat approach with all participants with available outcome data [37]. For those with missing follow-up data, we will compare the frequency and participant characteristics to determine differential loss to follow-up (LTFU). We will also carry out sensitivity analyses using last observation carried forward method, first by using 12 and 24-month research data, and second by using FPG or HbA1c available from routine clinic monitoring [38]. *Model 1*: We assume background rate of progression of 46.9% over 3 years, based on risk factors in the PRuDENTE cohort, INCMNSZ's cohort and the few other studies of low income or Hispanic individuals [12]; for LSO, because of lower intensity than efficacy trials, we assume a 20% reduction relative to background rate, yielding T2D prevalence of 37.5%. We assume LTFU rate of 27% and intra-class correlation of 0.03 [39]. With an a (two-tailed) = 0.05, and a β = 0.2, our sample of 3020 participants will yield a minimal detectable difference in the proportion with T2D between LS+M vs. LSO of 15% (prevalence 31.9% vs. 37.5%; RR 0.85). *Model 2*: We assume a background rate of progression at 3 years of 30.1% [7,40], yielding T2D prevalence of 24.6% in LSO and a minimal detectable difference in the proportion who have T2D between LS+M vs. LSO of 20% (prevalence 20% vs. 24.6%; RR = 0.8).

2.17 Implementation evaluation

We will apply the Reach, Effectiveness, Adoption, Implementation and/or Maintenance (REAIM) framework [41–44], to estimate uptake of, and variation in, PRuDENTE implementation processes. Box 2 contains a list of potential implementation processes and RE-AIM-related domains, that we intend to assess at the level of each clinic site for each intervention arm.

The RE-AIM framework has been widely applied to clinical prevention-focused interventions and includes measures of: reach across a target population; effectiveness; human and operational factors that promote adoption; and health-system factors that ensure maintenance. Implementation evaluation outcomes will be relevant to a wide range of primary care settings focusing on similar screening and treatment approaches for T2D prevention. We will explore moderating factors that may affect fidelity, using an adapted fidelity framework [45–48]. Together, these implementation and fidelity measures will allow us to understand which factors impact reach, effectiveness, and adoption across clinics, clinicians, and participants.

2.18 Implementation science framework example: Pre-intervention reach and adoption

As shown in Table 3, for step 1 we examine the proportion with risk factors assessed for eligibility for screening by the NDE. This allows us to estimate proportions screened and the

proportion that screen + and progress to step 2. Variation in these indicators will be estimated at patient (age, BMI, sex), clinician (work days/week, age, sex), and clinic levels (neighborhood deprivation index, size). For step 2, we examine the proportion who receive IFG test after referral, time between eligibility assessment and screening, and referrals made according to the assessment protocols. For step 3, we measure the proportion: with prediabetes, given their diagnosis after testing, and complete all study enrollment procedures, and compare these proportions by demographic, clinician and site characteristics. The adoption of diagnosis and enrollment procedures will be estimated, as well as timeframe to complete intervention enrollment activities. We analyze these data monthly using the PRuDENTE database.

2.19 Implementation fidelity

Implementation fidelity is critical to internal and external validity of translational research. [47] Without it, accurate conclusions about an intervention cannot be drawn, as unknown factors may have influenced outcomes. We combine quantitative and qualitative methods to measure fidelity to PRuDENTE components.[49] This embedded implementation study provides insights into how health services can be organized to translate T2D prevention interventions into primary care in a large public-sector health system, for what is a complex intervention.[50] We will first measure the fidelity with which the PRuDENTE intervention components for both arms were implemented by analyzing quantitative data, such as visit attendance and physician documentation of medication adherence. We will then use these results to characterize 'high' and 'low' fidelity sites. To improve understanding of the context of these findings, we will sample NDEs and PCPs for in-depth interviews at these sites. Interviews will explore barriers and enablers to PRuDENTE pre-implementation and intervention processes, and draws upon existing interview guides for evaluation of individual, system, and contextual factors that affect adoption and fidelity.[50,51] We developed a fidelity framework with core components, moderators, evaluation steps and outcomes. We ask the following questions: How much does delivery of core components vary by time and by characteristics of clinicians and clinics (quantitative data)? What are barriers and enablers to fidelity, across high and low fidelity clinicians and sites (qualitative data)? For quantitative assessments of fidelity to intervention components, we will use the PRuDENTE database and conduct evaluation of fidelity measures at intervention completion. We will analyze quantitative process metrics re completion or noncompletion of each component for all participants. Additionally, for the qualitative assessment, we will focus on observation and in-depth interviews with a purposive subsample of clinicians based on our analysis of fidelity measures. For each selected site, we will observe clinician interactions with participants over a week, and interview clinicians, in 10 high and 10 low fidelity sites, using rapid ethnography techniques.[52] These data will allow us to characterize variation in reach and contextual factors associated with high and low fidelity sites regarding intervention components. Mixed methods approaches will allow us to contextualize quantitative fidelity findings by exploring individual, clinic, programmatic, and policy-related barriers and facilitators, and incorporate qualitative findings into subsequent program recommendations.

2.20 Cost-effectiveness evaluation

The economic evaluation focuses on the incremental cost-effectiveness of LS+M vs. LSO, under the healthcare sector and societal perspectives in Table 4; and disparities between Mexican-origin and White populations in California. While we will track disparities in T2D incidence as the main outcome of the trial, our cost-effectiveness analyses will take into account projected differences in T2D incidence, prevalence, incidence of microvascular and macrovascular complications of T2D, and related healthcare costs. For the Mexico context, these secondary data are publicly available from a number of sources including the Ministry of Health in Mexico City. Due to the lack of availability of such data related to employers' costs and productivity costs the Mexico cost-effectiveness analysis will not include indirect costs. Our cost-effectiveness evaluation leverages our two validated models: a model of obesity, T2D risk and T2D microvascular complications ("Stanford model")[53] and a model of cardiovascular disease with and without T2D, including coronary heart disease and stroke (the "UCSF cardiovascular disease [CVD] model") [54]. Both models have been tailored and validated in the Mexican population and in US Mexican American adults, establishing feasibility[55,56] for outcomes of T2D complications and CVD endpoints.

The economic strategy in this study conforms to the 2016 recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses [57,58]; these substantively changed the structure, requirements, and implementation of cost-effectiveness analyses as compared to prior standards. Of note is that previously popular agent-based modeling methods fail to conform to standards required of the new guidelines, as they lack the external validation, reproducibility or transparency, and are at high risk for over-fitting and identifiability errors (having too many parameters estimated from too little data) [59]. New guidelines for cost-effectiveness analysis also require an "Impact Inventory" that specifies the analytical data to be included in two sub-analyses for each larger cost-effectiveness analysis: one analysis conducted from the perspective of public health and/or healthcare sectors, and the other from the perspective of broader society (including non-health sector actors such as taxpayers). Table 4 provides our impact inventory, assessing key pathways in our framework.

2.20.1 Cost-effectiveness conceptual framework—Our model (Figure 3) highlights both health- and non-health-sector influences on major factors affecting and affected by the primary interventions. The conceptual framework incorporates economic and health influences on these actors, including feedback loops among actors. It enables us to identify features of the intervention (LSO and LS+M), features of patients (adherence, co-morbidities), and features of the healthcare system (accessibility, provider adherence, infrastructure) that we conceive of as potentially influential to the health and economic impact of the intervention over the long-term.

2.20.2 Extrapolating the cost-effectiveness to US context—As there likely are residual differences between Mexican and Mexican American populations in T2D prevalence, socio-economic status, health-related exposures, and health behaviors, we will address discrepancies between the populations and quantify variation in how interventions may result in different effects between the two populations. To address this concern, we will

perform two modeling strategies. First, we assess how variations between the Mexican American population in the National Health and Nutrition Examination Survey (NHANES) and the Mexican National Health and Nutrition Survey (ENSANUT, by its Spanish acronym) differ explicitly in their recorded health exposures and (pre-)diabetes relevant measures [64,65], as well as compare such measures in PRuDENTE baseline questionnaire and diabetes-prevention surveys we have carried out with Mexican Americans in California's safety net. We will then model the dependency between demography and exposures and intervention effectiveness using the method known as targeted maximum likelihood estimation [66,67]. which involves a "transportability formula" that examines the degree to which the effect size observed in one population would be expected to have a different effect size in another population [68–70]. The approach can additionally bound the effects of unobserved/unmeasured confounders to help the modeling effort to identify the generalizability and applicability of our findings to a broader population of interest [71,72]

3. Discussion

The present study protocol describes a pragmatic cluster-randomized controlled trial of a LSO or LS+M intervention, with the aim of preventing or delaying T2D onset. The intervention is being conducted among obese Mexican adults with prediabetes ages 30-65 registered through *Seguro Popular* in Mexico City. A major contribution of this pragmatic trial is the identification of the main obstacles that primary care units in resource-constrained settings may face when implementing diabetes prevention programs. A list of pre-specified barriers will be intentionally explored and their potential impact estimated. The information gained from this trial may therefore inform the approach in which diabetes prevention programs should be implemented.

We developed age-related inclusion criteria based on the fact that prior studies have shown that Metformin is much more effective (<50% reduction) among patients with prediabetes age <60 and at best only marginally effective among older populations [7]. Furthermore, the public health value of preventing T2D among older populations is less apparent given competing mortality risks over the 10-20-year timeframe in that age group. Finally, Mexico has a rapidly growing population who develop diabetes before the age of 40 (early-onset diabetes) [73]. This trial will also allow us to explore incidence rates by age strata and evaluate if the intervention has differential effects (and cost-effectiveness implications) among younger adult populations. An important difference between our effectiveness study sample compared to previously randomized controlled efficacy studies is the inclusion of subjects with IFG, instead of IGT. Although this inclusion criterion may lead to a lower rate of incident diabetes [74], we added a BMI above 30 kg/m^2 as an obligatory additional inclusion criterion. This decision reflects the fact that (1) the combination of these two variables is associated with a higher risk of progression and sensitivity to diabetes prevention interventions, and (2) HbA1c testing is not routinely available to a majority of primary care clinics in *Seguro Popular* the two-hour oral glucose tolerance test is infeasible to administer on a large scale. That we are able to collect HbA1c tests from all participants at baseline will make it possible to examine both progression rates and Metformin effectiveness among those who have IFG +/− prediabetes-level HbA1c levels. In addition, another important difference of our intervention compared to previous DPP-based

interventions is that the lifestyle intervention involves counseling only, and is less intensive. Consistent with the objectives of a pragmatic clinical trial, this simple lifestyle intervention was designed in collaboration with the Ministry of Health based on feasibility related to local health system capacity and perceived acceptability to the patient population. It involves delivery of one 45-minute session at baseline and 12 15-minute sessions over three years. Since the efficacy of this intervention is likely to be lower than that of more intensive DPP-like interventions, future results will reflect the incremental effectiveness of Metformin beyond a simple lifestyle counseling intervention.

This study will also examine a range of implementation process outcomes at the clinic-, clinician- and patient-levels to inform our interpretations of effectiveness and enable efforts to refine, adapt, adopt and disseminate the model. While we were able to build in a qualitative component to understand the implementation fidelity issues faced by practitioners, we lacked the resources necessary to apply a parallel approach with patient participants, thereby limiting our implementation (RE-AIM) evaluation. Our study is also unique in its attempts to assess the cost-effectiveness of Metformin as an incremental intervention and extrapolate findings to Mexican Americans in the US context. Because interventions that prevent T2D may require the accrual of a significant amount of time before cost savings are realized, we needed to access secondary data and employ modeling techniques to project 10- and 20-year costs. We acknowledge that this timeframe may underestimate costly outcomes such as longer-terms complications and mortality. Furthermore, our inability to measure indirect costs in the Mexico City context will likely generate cost-effectiveness estimates that are conservative. Nevertheless, findings from the cost-effectiveness analysis will better inform how public delivery system costs compare to long-term costs averted by T2D delay or prevention in Mexico and among Mexican-origin adults living in the US.

The value of pragmatic clinical trials lies in their ability to generate a high degree of external validity. Yet, for studies in "real-world" settings, there are limitations and challenges. First, we were unable to design the study with a 3rd (control) arm that receives neither LSO nor metformin only. Because effectiveness studies demonstrate the unequivocal benefits of intensive lifestyle counseling, we considered it unethical to withhold a LSO intervention that is evidence-based. Because of the duration of interventions, a "wait-list" design was not feasible. And third, we are unable to carry out a non-inferiority trial comparing metformin alone to LS+M due to ethical concerns and because it is premature and cost-prohibitive.

As with any pragmatic clinical trial, and especially one carried out in overextended, public primary care clinic settings, we anticipate that many potential implementation barriers may emerge. These include attrition at the clinic and patient levels, inconsistencies in implementation fidelity by clinics and clinicians, patient non-adherence to clinic visits and/or PRuDENTE interventions, periods of unavailability of clinic personnel, laboratory assays/reagents or metformin at the MxCMoH level, lower quality or shortened visits due to busy clinics. Given the multi-step and longitudinal nature of primary care-based 2D prevention, the fixed capacity of public primary care settings, and the limitations and competing demands faced by low-income patients in Mexico City, we designed the evaluation to be able to measure implementation fidelity and evaluate possible barriers.

Understanding the degree to which a well-designed T2D prevention trial plays out in the real world will be of great value and benefit for health system planning for scaling T2D prevention programs in the future.

T2D was declared a national emergency by the Mexican Government due to the high incidence, poor prognosis and rise in diabetes mortality. In 2015, a T2D expert forum[8] convened to discuss key challenges with implementing and scaling up T2D prevention interventions based on the extensive evidence that T2D can be prevented or delayed among prediabetic populations. It is notable that, for low income populations, lifestyle changes associated with the DPP lifestyle arm are particularly challenging if not impossible to achieve. High rates of food insecurity and limited incomes among poor populations make it difficult for many individuals to consume more healthy foods and beverages. Furthermore, competing demands, and lack of recreational time and resources, often make it difficult to achieve physical activity goals needed to prevent T2D. In the absence of significant social, economic and environmental policy change, T2D prevention strategies that do not rely on lifestyle changes, such as therapy with metformin, will be critical to prevention efforts.

Understanding whether primary care interventions that use metformin is critical to controlling the T2D-related health emergency that Mexico and many other low- and middle-income countries across the globe are currently experiencing. Metformin is inexpensive, safe, generally well tolerated potentially enhancing its acceptability to many populations. Lastly, because Mexico has a national healthcare system with primary care centers similar to those in the US safety net, findings will not only generate considerable new translational knowledge to inform health policy in Mexico, but will also yield novel insights critical to advancing primary care-based T2D prevention for Mexican Americans in US public delivery systems, and for vulnerable populations globally.

Contributions

Luis A. Rodriguez and Dean Schillinger jointly drafted and revised the manuscript; Dean Schillinger, Simon Barquera, Carlos A. Aguilar-Salinas and Jaime Sepulveda-Amor designed the research; Jaime Sepulveda-Amor obtained funding and contributed to the draft; Simon Barquera and Carlos A. Aguilar-Salinas revised the draft; Edgar Denova-Gutierrez and Nydia Balderas critically revised the draft; Luz Maria Sanchez-Romero and Lizbeth Moreno-Loaeza participated in the design and implementation of the training sessions, in the acquisition of the data and selection of the participating centers and revised the draft; Margaret Handley designed the implementation evaluation and contributed to the draft; Sanjay Basu designed the cost- effectiveness evaluation and contributed to the draft; Oliva López-Arellano and Alberto Gallardo- Hernandez obtained funding, obtained ethics approval from the Mexico City Ministry of Health to implement the study, and revised the draft; All authors reviewed the article and contributed to its final form.

Acknowledgments

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Box 1

Inclusion and exclusion criteria.

Inclusion criteria

- Impaired fasting glucose of 100-125mg/dL

- 2 clinic visits in prior 12 months

- Registered with *Seguro Popular*

- Ages 30-65 years

- BMI 30kg/m^2

Exclusion criteria

- Prior diagnosis of diabetes

- Taking metformin, ora known allergy to metformin

- Pregnant women

- Diagnosis of active alcoholism or substance abuse

- Renal insufficiency (prior diagnosis, oreGFR <30 mL/min/1.73 m^2 or serum creatinine >2.0 mg/dL)

- Hepatic insufficiency (prior diagnosis of cirrhosis or hepatic enzymes >3x normal [ALT >180 U/L, AST >126 or GGT >207 among men and >111 among women])

Box 2

### Implementation domains to assess

- Patient screening/eligibility

- Clinic adoption/clinic retention

- Clinic visit scheduling adherence

- Patient (monthly/tri-monthly) visit attendance

- Clinician intervention delivery adherence

- Clinician monitoring adherence (medical and lifestyle adherence items and blood work)

- Metformin availability

- Lifestyle counseling delivery

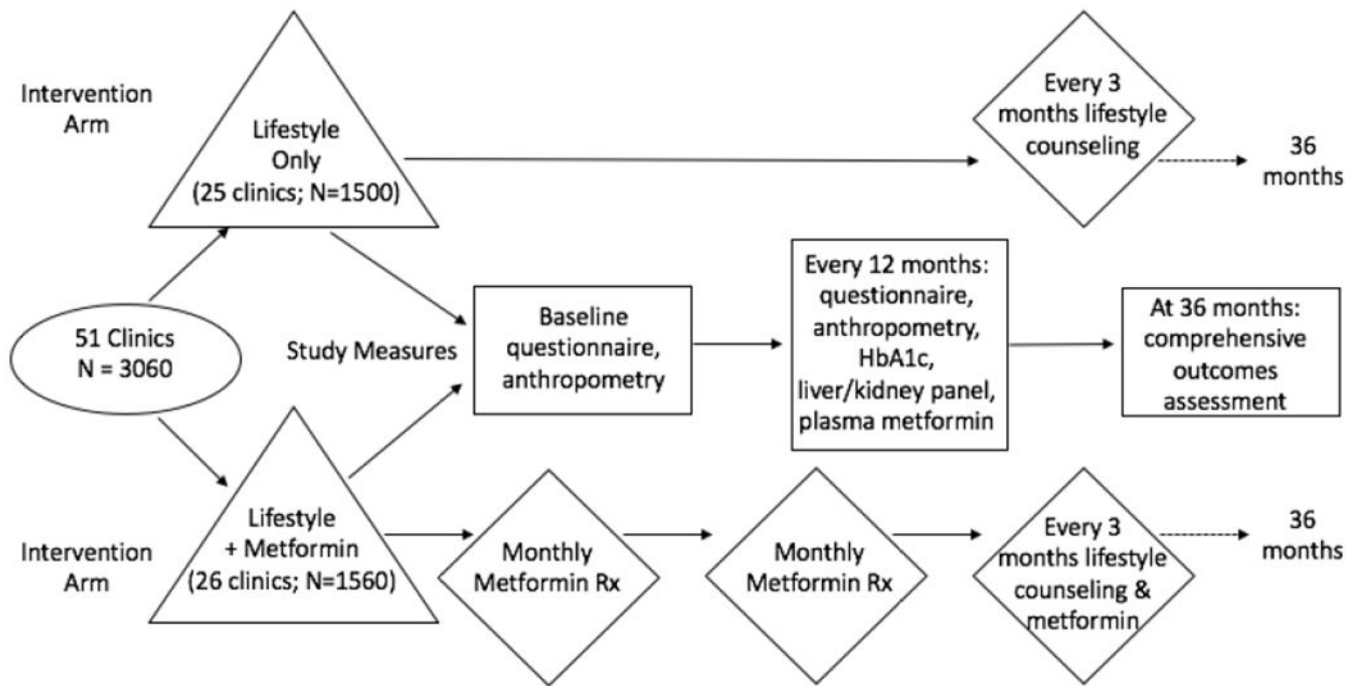- Patient intervention adherence (receipt of LSO or LS+M)

- Patient retention
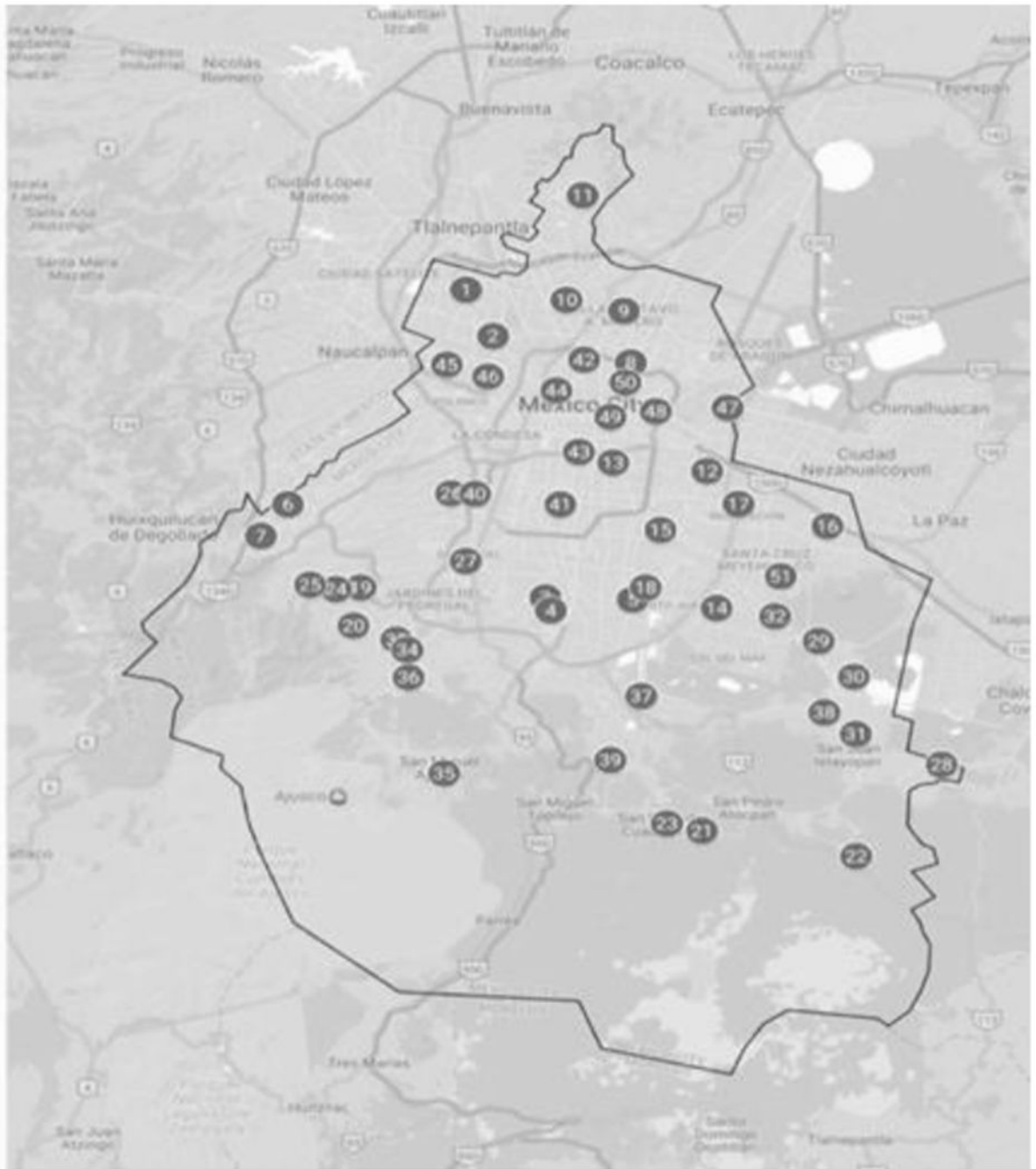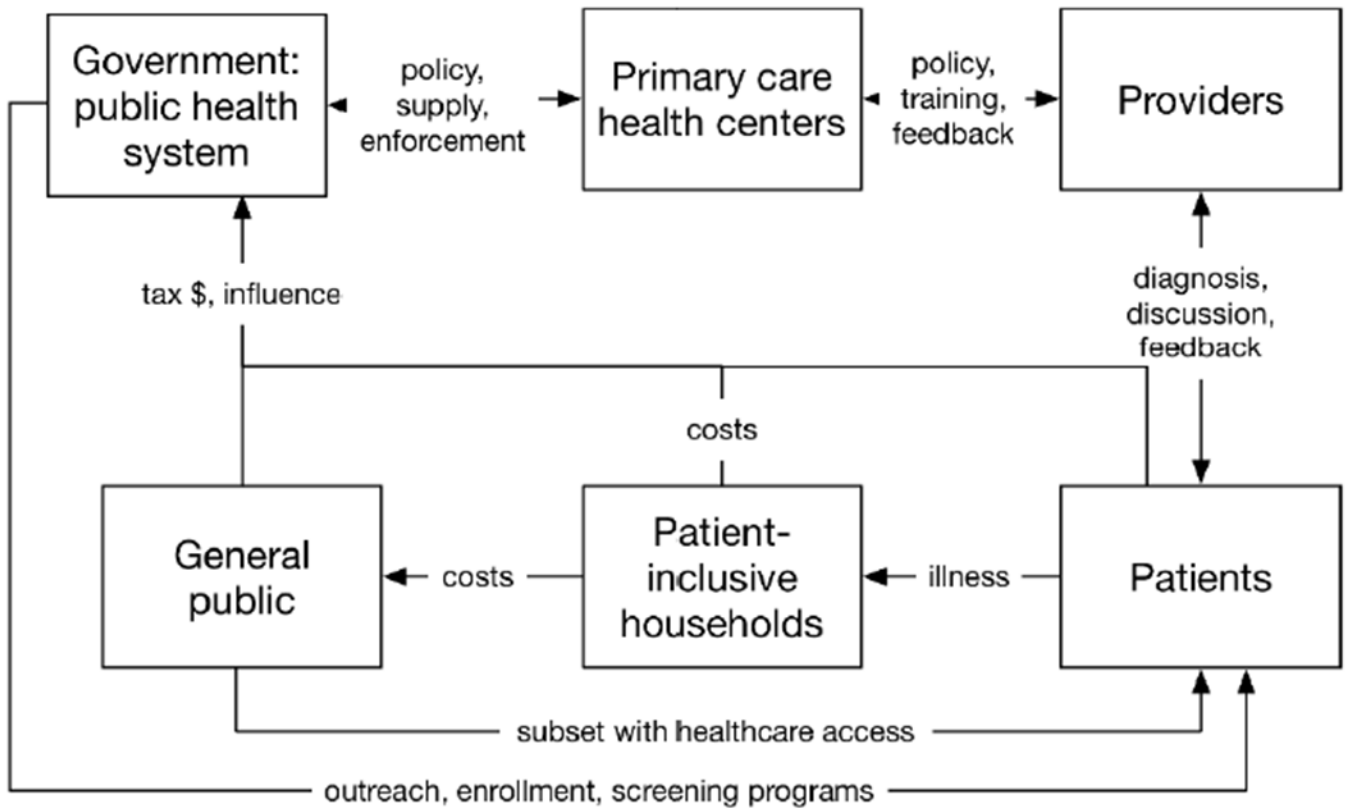
Figure 1.
Geography distribution of the 51 PRuDENTE clinics

Figure 2.
Design of the cluster-randomized controlled trial: PRuDENTE.

Figure 3.
Conceptual diagram for our cost-effectiveness evaluation

Table 1.

Study Measures (months)

Item	0	12	24	36
Blood[1]				
Fasting glucose and insulin	x	x	x	x
HbA1c	x	x	x	x
Fasting lipid panel	x	x	x	x
Liver and kidney panels	x	x	x	x
Vitamin B12	x			x
Plasma Metformin[2]		x	x	
Urine[1]				
Microalbuminuria	x	x	x	x
Anthropometric and clinic measures				
Blood pressure	x	x	x	x
Weight, height, and BMI	x	x	x	x
Waist and hip circumferences	x	x	x	x
Interviews/Questionnaires				
Adherence to metformin Rx[3]	x	x	x	x
Food frequency	x	x	x	x
Food insecurity	x	x	x	x
Physical activity	x	x	x	x
Contact and sociodemographics				
Tobacco and alcohol use	x	x	x	x
History of hypertension, obesity, hyperlipidemia, heart disease (self-report and chart review)	x	x	x	x
Family history of diabetes in 1st degree relatives	x	x	x	x
Current medication use (self-report and chart review)	x	x	x	x
Lifestyle changes self-efficacy	x	x	x	x
Quality of life	x	x	x	x

[1] Biomarkers are analyzed centrally at the Salvador Zubiran National Institute of Medical Sciences and Nutrition

[2] In LS+M arm, all 12- and −24-month samples will be included; a 10% random sample from LSO arm will also be included.

[3] Applies to patients on LS+M arm only; in addition, adherence is measured monthly.

Table 2.

PRuDENTE Outcomes

	Outcome	Definition
Primary	Incidence of T2D at 36 months	FPG 126mg/dL or HbA1c 6.5%
Secondary	Change in glycemia	HbA1c (continuous)
	Change in anthropometry	Weight, BMI, and waist circumference
	Change in physical activity	Self-reported average MET-hours/week, over 3 months
	Change in energy intake and dietary quality	Calculated from repeated food FFQ's

Table 3.

Implementation process measures related to 3 pre-intervention steps: 1) eligibility assessment; 2) offering of screening glucose and 3) disclosing impaired fasting glucose diagnosis and enrolling in PRuDENTE.

Step/RE-AIM Process Measure	Implementation Process Measures at each Pre-PRuDENTE Enrollment Step		
	Risk Eligibility → Assessment (Step 1) Compared by site, patient characteristic, clinician moderators	Offering of Glucose → Screening (Step 2) Compared by site, patient characteristics, clinician moderators	Diagnosis, Enrollment in PRuDENTE (Step 3) Compared by site, patient characteristics, clinician moderators
Reach Who gets 'in'?	*Patients*: Proportion of patients with either BMI>30 and age 30-65 years who are offered glucose testing.	*Patients*: Proportion of risk screen positives who received a referral for fasting glucose test.	*Patients*: Proportion of glucose tested patients who are given diagnoses of prediabetes; proportion of risk screen eligible patients who are given diagnosis of prediabetes; proportion with diagnosis who agree to participate in PRuDENTE
Adoption Did clinician, nurse, site complete phase activity?	*For each study nurse and clinician*: Proportion of patient visits with recorded data on risk eligibility (as defined by screening) in the database each day during enrollment.	*For each study nurse and clinician*: Proportion of patient visits with documentation that glucose test referral was given in the database each day during enrollment. *Sites*: Proportion of sites with complete referral data documented each week.	*For each study nurse and clinician*: Proportion of patients (diagnosis + and diagnosis −) given the fasting glucose test results within 48 hours; proportion offered PRuDENTE, if PRuDENTE-eligible; proportion of patients they attempted to enroll into PRuDENTE Sites: Proportion of nurses/clinicians completing enrollment materials within one week of test results (consent, survey, tests, labs ordered).
Adoption Did patient complete phase activity?	*Patients*: Proportion of patients who were able to provide adequate responses to screening questionnaires each day during enrollment.	*Patients*: Proportion of risk screen positives who complete fasting glucose test; proportion within 48 hours. Variation in test completion by demographic, clinician, and clinic measures.	*Patients*: Proportion of patients who agree to PRuDENTE who then complete all preintervention tests. Variation in enrollment by demographic, clinician, and clinic measures.
Data collection for each step	**DATABASE↑ Review/Site Metric feedback**	**DATABASE↑ Review/Site Metric feedback**	**DATABASE↑ Review/Site Metric feedback**

Table 4.

Impact inventory, corresponding to current (2016) updated guidelines for cost-effectiveness analysis [57,58]

Sector	Type of im pact	Data in analysis from Data in analysis from societal perspective he alth s ector pe rs pective
Formal Healthcare Sector		
Health	*Health outcomes (effects):*	
	Longevity effects	Mortality attributable to obesity, T2D and its complications (Stanford model), and cardiovascular disease (UCSF model), from vital statistics data [60,61]
	Health-related quality-of-life effects	QALYs from microvascular diabetes complications (Stanford model); from obesity complications unrelated to diabetes (Stanford model); and from cardiovascular disease w/ or w/o diabetes (heart disease and stroke; UCSF model), from Tufts CEA Registry [62]
	Other health effects (e.g., adverse events)	QALYs from pharmaceuticals for diabetes (Stanford model); and for cardiovascular disease (UCSF model), from Tufts CEA Registry [62]
	Health-related costs:	For prediabetic patients under the intervention: Direct health care costs for each arm: health staff costs (salaries and type of staff required in each arm, estimating specific time spent exclusively with pre-diabetes patients, drugs; laboratory tests; training; operation and capital costs (weighted by the proportion of pre-diabetes patients over total patients at the facility).Source of information: data collection at the facilities
	Raid for by third-party payers	Private and public (primary care health centers) costs from obesity and T2D (Stanford model) and from CVD (UCSF model), populated with data from partners
	Raid for by patients out-of-pocket	For prediabetic patients during the intervention -Out of pocket expenditures (health expenses not covered by *Seguro Popular:* drugs, laboratory tests. etc.), transportation cost.Source of information: data will come from a short questionnaire (exit interview applied to a random sample of patients in the intervention over the 3 years). For patients that develop T2Ds: out of pocket expenditures from Mexican surveys (National Health and Nutrition Surveys, National Income and Expenditure Surveys and *Seguro Popular* Survey)Co-payments for visits and over-the-counter pharmaceuticals, populated with Aim 2 process evaluations
	Intervention-related public health or medical costs (payers and population)	Aim 2 cost estimates for implementation (for public health and clinic levels), costs borne by patients, and non-research-related personnel, materials, and resource costs in Mexico
	Future unrelated medical costs (payers and population)	Competing risks algorithm for unrelated age- and sex-specific morbidity- and mortality-related costs, populated with vital statistics data [61]
Non-Health Sectors		
Productivity and costs	Labor market earnings lost N/A	Diabetes-related losses from Work Productivity and sector (Stanford model)
	Cost of unpaid lost productivity due to illness N/A	
	Cost of household consumption changes	Losses of household earnings (absenteeism, job loss) due to diabetes (Stanford model)

Abbreviations: Tufts CEA Registry: Tufts University Cost-effectiveness Analysis registry; QALYs: quality-adjusted life-years