

Official Title: The Breakfast Study: A Small Steps, Low-literacy, Breakfast-focused Dietary Self-management Intervention for Adults With Poorly Controlled Type 2 Diabetes

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ABSTRACT

More than 15% of U.S. adults with type 2 diabetes have poorly controlled blood glucose, here defined as a glycated hemoglobin (HbA1c) level of 7.0% or higher. These adults have an elevated health risk of a variety of outcomes, including amputation and mortality from cardiovascular disease and from all causes. Nutrition-focused interventions can be effective for improving glycemic control, reducing anti-hyperglycemic medications, and reducing body weight, all of which are critical outcomes for adults with type 2 diabetes. Carbohydrate intake has the strongest impact on post-prandial glycemia of any dietary factor, and a very low-carbohydrate diet—due to its ability to improve glycemic control—is now recommended by the American Diabetes Association (ADA) for the treatment of type 2 diabetes. However, typical nutrition-focused interventions can be burdensome, often requiring complex instructions and a complete overhaul of one's diet. Additionally, adults with poorly controlled type 2 diabetes are more likely to have low health literacy levels, which can be a barrier for adherence to complex interventions. Therefore, an effective intervention for adults with poorly controlled diabetes who may have lower health literacy levels is necessary to reduce both HbA1c levels and anti-hyperglycemic medications. The benefits of a very low carbohydrate diet may be available to individuals who change only their breakfasts to match this dietary pattern, rather than modifying their entire diet. We hypothesize that a digital, small-steps, low-literacy very low-carbohydrate breakfast-focused program for adults with poorly controlled type 2 diabetes could be such a program. Thus, we propose an acceptability, feasibility, preliminary effectiveness trial in up to 123 adults with poorly controlled type 2 diabetes. We will assign adults with an HbA1c of 7.0% or higher to our online, 4-month intervention, which will teach participants to change their breakfasts to be very low-carbohydrate. We will measure acceptability and feasibility, plus critical efficacy outcomes, such as changes in HbA1c, anti-hyperglycemic medications, glycemic variability, body weight, blood pressure, and lipids. We will also test whether factors such as sex, health literacy level, and baseline insulin resistance significantly moderate the impact of the intervention on change in HbA1c and change in anti-hyperglycemic medications. These moderation analyses will contribute to a nascent research approach for personalized nutrition, which responds to Objective 2-5 of the NIH's May 2020 Strategic Plan for NIH Nutrition Research. This submission is in response to PAS-20-160, Small R01s for Clinical Trials Targeting Diseases within the Mission of NIDDK, which does not require preliminary data. If results are promising, our goal is to conduct a follow-up, powered, longer randomized trial of this approach. As the prevalence of type 2 diabetes and the understanding of personalized interventions continue to increase, there is a critical need to provide additional effective options for population-level type 2 diabetes treatment strategies, especially for adults with poorly controlled type 2 diabetes.

PROJECT NARRATIVE

This work aims to help improve health outcomes for adults with poorly controlled type 2 diabetes by testing a potentially effective breakfast-focused self-management intervention. We hypothesize that this will be a feasible and effective option.

SPECIFIC AIMS

More than 15% of U.S. adults with type 2 diabetes have poorly controlled blood sugar, here defined as a glycated hemoglobin (HbA1c) level of 7.0% or higher.¹ These adults have an elevated health risk of a variety of outcomes, including amputation² mortality from all causes and from cardiovascular disease.³

Nutrition-focused interventions can be effective for improving glycemic control, reducing anti-hyperglycemic medications, and reducing body weight, all of which are critical outcomes for adults with type 2 diabetes, especially those with poorly controlled diabetes. However, typical nutrition-focused interventions can be burdensome, often requiring complex instructions and a complete overhaul of one's diet. Furthermore, existing digital health diabetes education programs, which are becoming the standard-of-care approach, are either similarly burdensome, or offer little improvement for adults with poorly controlled type 2 diabetes. Additionally, adults with poorly controlled type 2 diabetes are more likely to have low health literacy levels, which can be a barrier for adherence to complex self-management interventions.^{4,5}

Therefore, an effective, simple, intervention for adults with poorly controlled diabetes, who may have lower health literacy levels, is needed to reduce both HbA1c levels and anti-hyperglycemic medications. We hypothesize that a digital, small-steps, low-literacy very low-carbohydrate breakfast-focused program for adults with poorly controlled type 2 diabetes could be such a program. Carbohydrate intake has the strongest impact on post-prandial glycemia of any dietary factor, and a very low-carbohydrate diet—due to its ability to improve glycemic control and reduce anti-hyperglycemic medications—is now recommended by the American Diabetes Association for the treatment of type 2 diabetes.⁶ The benefits of a very low carbohydrate diet may be available to individuals who change only their breakfasts to match this dietary pattern, rather than modifying their entire diet. For example, in a 3-month randomized trial of 59 overweight or obese adults with type 2 diabetes, those assigned to eat a higher-calorie, reduced-carbohydrate breakfast had greater reductions in HbA1c and anti-hyperglycemic medications than those assigned to eat a smaller, higher carbohydrate breakfast.⁷ However, participants' average baseline HbA1c level was 6.9%, so their type 2 diabetes was already well controlled. In a feeding trial of 23 adults with type 2 diabetes, participants ate isocaloric diets, varying only in whether or not the breakfast was very low-carbohydrate or higher carbohydrate. On the days that participants consumed the very low-carbohydrate diet breakfast, their morning postprandial hyperglycemia was eliminated and their before-dinner perception of hunger was lower.⁸ Additionally, in a recent quality improvement project, 19 older, lower literacy veterans, all on insulin, were taught to eat a lower carbohydrate, higher protein breakfast. The veterans' HbA1c was reduced by a unit of 1.5% and overall insulin medication levels were reduced, as well. Such results are promising and warrant further study.

Thus, we propose an acceptability, feasibility, preliminary effectiveness trial in up to 123 adults with poorly controlled type 2 diabetes. We will assign adults with an HbA1c of 7.0% or higher to our 4-month, digital, small-steps, low-literacy very low-carbohydrate breakfast-focused program (The Breakfast Study).

- **Aim 1: Assess acceptability and feasibility.** We will examine intervention acceptability and feasibility, including participants' satisfaction with the intervention and their diabetes treatment, health-related quality of life, class attendance, and dietary adherence.
- **Aim 2: Assess changes in health and psychological outcomes.** We will assess health and psychological outcomes, including HbA1c, anti-hyperglycemic medications, glycemic variability, body weight, lipids, insulin resistance, blood pressure, self-efficacy for dietary adherence, and satiety.
- **Aim 3: Assess factors that identify individuals who will particularly benefit from the intervention.** We will test whether factors such as sex, health literacy level, emotional eating, and baseline insulin resistance significantly moderate the impact of the intervention on change in HbA1c. These moderation analyses will contribute to a nascent research approach for personalized nutrition, which responds to Objective 2-5 of the NIH's May 2020 Strategic Plan for NIH Nutrition Research.

This submission is in response to PAS-20-160, Small R01s for Clinical Trials Targeting Diseases within the Mission of NIDDK, which does not require preliminary data. If results are promising, our goal is to conduct a follow-up, powered, longer randomized trial of this approach. As the prevalence of type 2 diabetes and the understanding of personalized interventions continue to increase, there is a critical need to provide additional effective options for population-level type 2 diabetes treatment strategies, especially for adults with poorly controlled type 2 diabetes.

RESEARCH STRATEGY

Type 2 diabetes is prevalent, costly, and especially problematic for adults with poorly controlled type 2 diabetes, and adults with poorly controlled type 2 diabetes are at even greater risk for poor outcomes.

Type 2 diabetes is one of the largest and most prevalent contemporary public health problems in the U.S.; if the current trajectory of prevalence continues, 1 in 3 U.S. adults will have type 2 diabetes by 2050.⁹ It is a chronic illness that can significantly reduce quality of life and lead to serious health problems, including heart attack, stroke, blindness, amputation, renal failure, and premature death. For example, over half of all amputations in the U.S. are due to complications from type 2 diabetes.¹⁰ It is the most expensive health condition in terms of total dollars spent nationwide¹¹ and these costs continue to grow: from roughly \$200 billion in 2007 to \$327 billion ten years later.^{12,13} More than 15% of U.S. adults with type 2 diabetes have poorly controlled type 2 diabetes.¹ These adults have an elevated health risk of a variety of outcomes, including amputation² and mortality from all causes and from cardiovascular disease.³

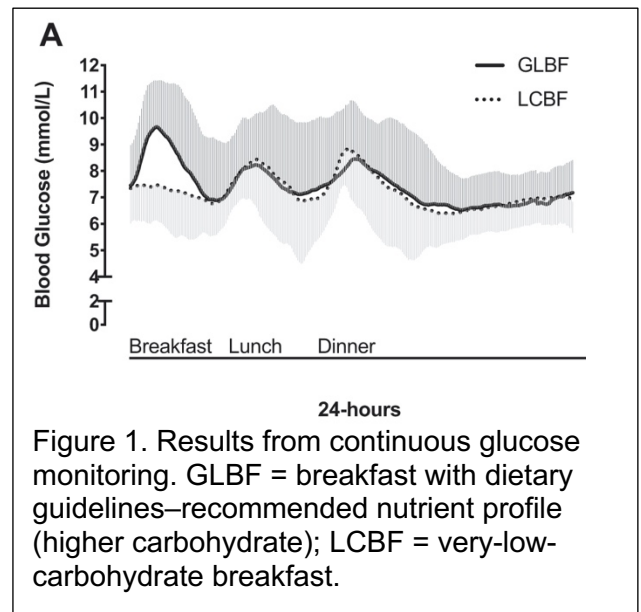
Previous research suggests that the simple change to consuming a reduced-carbohydrate breakfast, can improve overall glycemic control, reduce the need for anti-hyperglycemic medications, reduce postprandial variability, and reduce hunger for adults with poorly controlled type 2 diabetes.

A recent large trial found that post-prandial glucose variability in response to a standardized breakfast predicts subsequent hunger and thus breakfast may be an important target for changing day-long eating behavior. Researchers tracked the continuous glucose responses of more than a thousand people and results showed a link between postprandial glucose and subsequent hunger and calorie consumption. Researchers found that larger blood glucose dips after eating led to greater later-day calorie consumption. This suggests that, by eating meals that reduce postprandial glycemic variability, subsequent hunger and therefore subsequent eating might be reduced. Additionally, they tested several types of standardized breakfasts with different macronutrient percentages. As expected, the lower-carbohydrate breakfast (25% of calories from carbohydrates) caused a blood glucose spike that was half that of the higher-carbohydrate breakfast (75% of calories from carbohydrates).¹⁴ While compelling, this trial occurred in people without type 2 diabetes, whereas previous research shows that people with type 2 diabetes have on average twice as large a blood glucose spike in response to eating carbohydrates, as compared to people without type 2 diabetes.¹⁵ This suggests that the importance of reducing carbohydrate consumption may be even more important for glycemic control in people with type 2 diabetes.

Similarly, a previous, small, short feeding trial found that a very low-carbohydrate diet breakfast reduced postprandial glycemic variability and subsequent hunger. In a trial of 23 adults with type 2 diabetes, participants were fed isocaloric diets, varying only in whether or not the breakfast was very low-carbohydrate (3% of calories from carbohydrates) or higher carbohydrate (52% of calories from carbohydrates). An example of a very low-carbohydrate breakfast was a spinach and cheese omelet with a coffee with cream; an example of a higher carbohydrate breakfast was a breakfast parfait with yogurt, oats, fruit, and pumpkin seeds with a coffee and 1% milk.

On the days that participants consumed the very low-carbohydrate diet breakfast, their morning postprandial hyperglycemia was eliminated (see Figure 1) and their before-dinner hunger was lower.⁸ In that study, participants were not allowed to deviate from the provided food, but the lower levels of hunger before dinner in the very low-carbohydrate diet breakfast group suggests that there might be a longer-term effect of reducing carbohydrates at breakfast, such that, with lower hunger, participants might naturally calorie restrict later in the day. Studies of *ad libitum* very low-carbohydrate diets, in which participants are instructed to eat when hungry and stop when full, find lower levels of hunger and lower levels of calorie consumption.¹⁶

Although results from the feeding trial were promising, the study examined results over just a couple of days. A longer trial is needed to understand long-term, real-world implications of a very low-carbohydrate



breakfast. A similar study was conducted over 3 months with 59 overweight or obese adults with type 2 diabetes. Participants were randomized to eat a higher-calorie, reduced-carbohydrate breakfast (39% of calories from carbohydrates) or a smaller, higher carbohydrate breakfast (55% of calories from carbohydrates). Those assigned to eat the reduced-carbohydrate breakfast had greater reductions in HbA1c and anti-hyperglycemic medications than those assigned to eat a smaller, higher carbohydrate breakfast. However, participants' average HbA1c level was 6.9%, so their type 2 diabetes was already well controlled, and the reduced-carbohydrate breakfast still had 39% of calories from carbohydrates and therefore would not be considered a very low-carbohydrate meal.⁷

Moreover, some collaborators of ours conducted a quality improvement pilot project teaching participants to eat a lower carbohydrate, higher protein breakfast. Suggested choices included lower carbohydrate options, such as eggs, full-fat Greek yogurt, and cheese (all of which have less than 20% of calories from carbohydrates), plus somewhat higher carbohydrate options, such as Ensure High Protein (48% of calories from carbohydrates). They also asked participants to avoid fruit juice, toast, muffins, donuts, and other sweets. In a sample of 19 older, lower literacy veterans, all on insulin, HbA1c reduced by a unit of 1.5% and overall insulin medication levels were reduced, as well (manuscript in preparation). Such results are promising and warrant further study.

Taken together, previous research suggests the benefit of a very low-carbohydrate diet breakfast for improving glycemic control, reducing the need for anti-hyperglycemic medications, reducing postprandial glucose variability, and reducing both subsequent hunger and calorie consumption.

Exploration of several potential moderators of the effect: the opportunity for personalized nutrition.

While we anticipate that this breakfast-focused intervention will lead to greater HbA1c reduction on average, individuals vary in their response to diets. We will test whether factors such as sex, health literacy level, emotional eating, and baseline insulin resistance significantly moderate the impact of the intervention on change in HbA1c and change in anti-hyperglycemic medications. To our knowledge, exploring these moderators is novel. Assessing potential moderators could help predict which type of diet is best for glycemic control for whom. These moderation analyses will contribute to a nascent research approach for personalized nutrition, which responds to Objective 2-5 of the NIH's May 2020 Strategic Plan for NIH Nutrition Research.

3. APPROACH

Proposed approach for specific aims. We propose to assign up to 123 adults with poorly controlled type 2 diabetes to our 4-month online intervention. Most assessments will take place at baseline and 4 months later, at the end of the 16-week program.

Participant recruitment. We will recruit based on methods from our previous research, including using online advertisements and mailings based on medical records. An initial search identified >120,000 adults in the Michigan Medicine medical records likely to be eligible based on age, HbA1c in the past year, and diagnoses. As we have done in previous research, we will initially contact the pool of potentially eligible participants by sending them a letter and flyer using a HIPAA-compliant company describing the study, which will refer them to a study web page and an initial online screening questionnaire. In previous research, this approach has been highly effective: more than 10% of patients that we mail a letter to then fill out our baseline screening survey. Considering the large number of participants with poorly controlled type 2 diabetes in our medical system, this approach should yield a more than sufficient supply of eligible participants.

However, if we find that any gender or racial/ethnic group is joining our study in an unrepresentative way (a much greater or smaller percentage than expected), we will alter who we target, contact, and/or include in the trial. We will contact potentially eligible participants from particular demographics, based on medical records, to correct this issue. We will also use social media, such as Facebook and Instagram, to target ads to particular demographics and work with the recruitment support program at UM's Michigan Institute for Clinical and Health Research (MICHR), to help recruit appropriate participants. Moreover, if enrollment lags significantly behind the original target, additional contingency plans include (1) contacting individuals directly via phone or email 2 weeks after the initial invitation letter is sent; (2) accepting direct referrals to the program from healthcare providers; (3) using flyers and advertising on a variety of other institutional websites, including the UMHealthResearch site; (4) using paid advertisements, including targeted ads on Google, YouTube, research engagement platforms, such as Altura Studies, CliniContact, Thrivable, Image Bloom and Policy Lab, and

social media websites; or (5) outreach to additional medical centers, including Federally Qualified Health Centers.

Eligibility. *Key inclusion criteria include:* poorly controlled type 2 diabetes, defined as a current HbA1c $\geq 7.0\%$; the ability to read and speak English; aged 18-80; and the willingness to regularly check blood glucose levels. *Exclusion criteria include:* unable to provide informed consent; pregnant or planning to become pregnant in the next 6 months, or breastfeeding or <6 months postpartum (pregnancy and breastfeeding require modifications to the intervention's dietary approaches); vegan (while it is possible to follow the proposed diets while following a vegan diet, it requires extensive modification of intervention materials); a C-peptide test result that suggests type 1 diabetes or a previous diagnosis of type 1 diabetes (adults with type 1 diabetes need an intervention appropriate for their particular needs and safety concerns); or triglyceride levels greater than 999 mg/dL.

Enrollment procedures. Potential participants will make initial contact with the study by visiting the study website or reaching out to the study team through a dedicated study phone number and/or email address. Participants will be directed to a study website where they will take an initial screening survey online. If participants remain interested, they will be invited to sign a consent for a blood draw. If they are eligible based on the screening blood draw results, then our study staff will consent them on the phone or via a video chat and review the study schedules, procedures, and assessments. Participants will then (1) complete a baseline survey, which can either be done online, on the phone, or through a video chat with our study staff; (2) watch an online video describing the study and answer questions about their goals for participation and pros and cons of participation (which previous research suggests can improve trial retention¹⁷); (3) participate in 1-2 24-hour dietary recalls over the phone, and (4) have a baseline fasting blood draw to assess parameters required for inclusion: HbA1c $\geq 7.0\%$ or higher, thyroid-stimulating hormone in a normal range, liver and kidney function in a normal range, and no indication of type 1 diabetes. Specifically, the baseline tests may include a comprehensive metabolic panel, a lipids panel (NMR LipoProfile+Lipids), HbA1c, insulin, thyroid-stimulating hormone, hsCRP, and C-Peptide. Participants who are taking insulin or who answer positively to at least 2 out of 4 Latent Autoimmune Diabetes in Adults (LADA) screening questions (listed below) will receive a C-Peptide test during this screening blood draw. If their C-Peptide is below 0.75 ng/mL, these participants will be ineligible. If their C-Peptide is between 0.75 ng/L and 1.5 ng/mL, these participants will need to return to LabCorp for an additional test, GAD65. If GAD65 results are positive, participants will be ineligible. Participants with a triglyceride level reported on the initial blood draw of 300-499 mg/dL will be enrolled with the requirement of a follow up NMR LipoProfile+Lipids test two weeks into the intervention. If triglycerides increase after two weeks of the intervention, the team will inquire about alcohol use, and recommend that the participant see their PCP for follow-up. For triglyceride levels 500-999 mg/dL, we will have the participant first discuss the result with their primary care physician so that any medication or dietary changes can occur before starting the study. If any significant changes were made by the participant's physician (e.g., addition or removal of a medication, change in alcohol consumption), we would measure a new baseline at the appropriate time. If triglycerides are greater than 999mg/dL, participant will not be enrolled. Such tests may also be ordered after an initial meeting with the study MD, based on clinical judgment.

1. Were you younger than 50 when you were diagnosed with diabetes? Note, if you are younger than 50 now, please answer yes.

2. When you were diagnosed with diabetes, what was your approximate weight in pounds? If you are unsure, give your best estimate of your weight in pounds at that time. How tall were you when you were diagnosed with diabetes?

3. Within the 6 months before you were diagnosed with diabetes, did you suddenly experience any of the following symptoms? Note, if you have always had a small bladder or have needed to urinate frequently, this does not apply. Again, we are interested in knowing whether you had sudden onset of any of the following symptoms right before you were diagnosed with diabetes.

Unintentional weight loss
Nausea, vomiting

Need for hospitalization to treat high glucose
Need to take insulin to manage blood glucose

4. Do you have any of the following conditions?

Autoimmune thyroid disease (i.e., an over- or underactive thyroid gland also known as Graves' or Hashimoto's disease)
Celiac disease (gluten allergy or intolerance)
Addison's disease
Pernicious anemia (vitamin B12 deficiency)
Vitiligo
Alopecia
Rheumatoid arthritis
Sjögren's disease
Autoimmune hepatitis

For participants whose baseline TSH out of range, we may optionally order free T3 or free T4 tests, or we may screen for TSH with a thyroid cascade profile (If TSH is <0.450 , the test will reflex to thyroxine (T4), free, direct and depending on the thyroxine (T4), free, direct result, may reflex to a triiodothyronine (T3), free. If the TSH is >4.500 , it will reflex to thyroxine (T4), free, direct and depending on the thyroxine (T4), free, direct result, may reflex to a thyroid peroxidase (TPO) antibody, both at an additional charge.) If participants' thyroid is managed, we may retest their TSH levels and include them in the trial if the levels are now in range.

Some of these may be repeated at 4 months, such as a comprehensive metabolic panel, a lipids panel (NMR LipoProfile+Lipids), HbA1c, insulin, and hsCRP. Participants may be ineligible after their fasting blood draw. If eligible based on blood tests, participants may come to a Michigan Medicine location to have a continuous glucose monitor (CGM) attached and may have their waist and hip circumference measured, as well as their weight and height. Or they may be mailed the CGM with instructions as to how to apply it themselves. The CGM monitor will provide no feedback to participants. After wearing the CGM for 14 days, participants will mail the device back to program staff. Participants at risk for hypoglycemia may be sent a glucometer and testing supplies in order to self-monitor their blood glucose over the course of the trial. Participants may receive a blood pressure cuff to self-monitor their blood pressure several times over the course of the study. Also, we may mail participants a scale to assess their weight throughout the intervention. Once all baseline steps have been completed, the program will begin asynchronously for each participant.

Intervention. Dr. Saslow has developed an online very low-carbohydrate (ketogenic) diet program for adults with type 2 diabetes to improve their glycemic control and help them lose weight and is optimizing this intervention through a K01 from NIDDK.¹⁸⁻²⁰ Dr. Saslow has also adapted this program and is currently testing it in other populations. This online program, in addition to being feasible, acceptable, and effective in other populations, allows us to conduct the intervention remotely. Intervention satisfaction is high. In our most recent trial among adults with hypertension, of the 80 participants who finished the trial, 94% said they would recommend it to a friend in similar need of help, and 90% rated their satisfaction as at least a 5 on a scale from 1 (*not at all satisfied*) to 7 (*very satisfied*). This breakfast-focused intervention builds upon that program and includes similar components and topics, described below. Participants will receive weekly classes online, cookbooks or recipes through the mail or via email, and a diet coach to support them along the way.

Participants will have the option to join monthly group calls online (video or audio) with the coach that may include other participants. Participants can email coaches at any time with questions and will receive responses a maximum of twice a week. Coaches will be in contact with all participants at least every other week throughout the program (regardless of whether or not they've received emailed questions from participants). All emails will be monitored for fidelity to intervention recommendations. All calls will be recorded and monitored for fidelity.

Very low-carbohydrate breakfasts. Materials will encourage eating a very low-carbohydrate breakfast each day. Most studies of very low-carbohydrate diets use an approach that focuses on food choices, without calorie counting or an effort to restrict calories, and we will take the same approach. We will recommend that breakfast meals should have no more than about 5-10 non-fiber grams of carbohydrates or no more than 20% of total calories from carbohydrates. To avoid confusion about how to interpret this, we will provide participants

copious food options from handouts, links, and cookbooks or recipes, which will vary in their complexity and cost. We will make it clear that simple-to-prepare, budget-friendly meals, such as scrambled eggs with cheese, are very feasible, but we will also provide a wide range of options. See Table 3 for examples. Through coaching, we will help participants to find options that they enjoy and find accessible, as we have done in our other very low-carbohydrate diet interventions.

Table 3. Example very low-carbohydrate diet breakfasts

Examples
Example breakfast components: • Varieties of very low-carbohydrate eggs meals: omelet with vegetables and cheese, scrambled eggs with avocado, deviled eggs, fried eggs, hard or soft boiled eggs, frittatas, and breakfast casseroles • Varieties of very low-carbohydrate waffles, muffins, pancakes, granolas, breakfast cereal, and bread • Burritos, made with low-carbohydrate tortillas • Very low-carbohydrate hash browns, such as those made from cauliflower, radishes, or zucchini • Coffee with added butter, coconut oil, or full-fat dairy • Very low-carbohydrate chia seed pudding • Very low-carbohydrate breakfast parfait with nuts and/or seeds, berries, and high-fat Greek yogurt
Components that are more like lunches that some people may prefer for breakfast: • Varieties of very low-carbohydrate soups • Cabbage stir-fry • Cheese rollups • Salad-wrapped sandwiches • Tuna-stuffed avocado • Sliced vegetables and dip • Sausage or bacon with creamed cabbage or spinach • Reheated very low-carbohydrate pizza, lasagna, or chili

Strategies to build self-efficacy and self-regulation. Drawing on ideas from both social cognitive theory and self-regulation theory, a recent review emphasized that dietary self-management programs should utilize strategies that can build self-efficacy and self-regulation.²¹ Indeed, self-management programs, such as the Diabetes Prevention Program,²² and our program, rely on these strategies, detailed below.

Building self-efficacy: mastery experiences. A primary way to increase self-efficacy is to create mastery experiences; enabling participants to succeed at a task, rather than fail.²³ This breakfast-focused program is thus designed to encourage participants to make a small and manageable dietary change.

Building self-efficacy: social modeling. Another way to increase feelings of self-efficacy is to have behaviors modeled by others, to help clarify how to implement them and to show how others have coped with social and emotional barriers to implementation.²⁴ Thus, the intervention includes many comments from others about the strategies they have used to overcome barriers to dietary adherence, as well as how the dietary changes have impacted them.

Building self-regulation: goal setting and self-monitoring. Goal setting is also informed by the control systems theory, which suggests that people are motivated to change a behavior when they become aware of the inconsistency between their goals and current actions and then attempt to reduce this inconsistency.²⁵ Thus, self-monitoring may increase behavioral adherence by providing participants feedback about how well they are achieving their goals.^{26,27} We will provide goals for target breakfast macronutrients including an in-depth menu of options. We will ask participants to then self-monitor their diet, particularly their breakfasts. They can either describe their breakfasts as part of the program's weekly check-in or they can use an application, such as the free online and mobile application, MyFitnessPal (which has a wide variety of foods in its database and over 150 million users). Participants may also be asked to self-monitor their weight at least weekly, their blood pressure at least weekly, and their blood sugar at least twice a day, depending on the glucose-lowering medications they are taking.

Building self-regulation: personalized feedback and support. Diet coaches can be effective at helping participants follow a new diet by providing personalized feedback and support.²⁸ Coaches will provide supportive messages about participants' progress, answer participant questions, and, based on participants' preferences, offer advice about new foods or recipes to try. As we have done in our previous research, coaches are trained using a coaching manual and all written coaching messages will be checked for fidelity to

the manual; coaches draw upon the coaching manual and also individualize responses as appropriate. Any topics the coach cannot answer are referred to the appropriate person on the research team for a timely, evidence-based response to the participant, sent through the coach. Participants will receive prompt replies from their coaches, and coaches will also reach out to participants at least every two weeks. Participants may interact with their coaches via phone, video, and/or email.

Remote format. The intervention is entirely remotely delivered and technology supported.

Asynchronous online classes. As in our previous research, participants will be sent links to the weekly content. The links connect them to: a) a short survey to assess intervention-related behavioral adherence and concerns (see below for more information), b) a video to teach the topics, c) downloadable handouts, d) mobile-friendly versions of the handouts and content, and e) links to resources. These asynchronous lessons can be watched and read at participants' convenience and take about 10–30 minutes to complete. We will track how often and when participants log into the lessons, allowing us to assess engagement with the curriculum.

Weekly check-in surveys and Quizzes

Every week, participants receive an email with the content and a short survey. They are incentivized monetarily to complete the survey every week for 16 weeks. A \$4 amount will be awarded per completed survey, added to their \$36 final gift card after completing the program, for a total of up to \$100.

Participants will receive this survey as part of their classes:

Welcome! Since the past check-in...

1. I ate a very low-carb/keto breakfast. 1 = not at all to 7 = very much so.
2. I enjoyed eating a very low-carb/keto breakfast. 1 = not at all to 7 = very much so.
3. If we asked you to measure your blood sugar levels for the study, what have been your lowest and highest blood sugar readings (mg/dL) over the past week? Please note whether they were fasting, before dinner, or other and whether you had any symptoms at the time of the measurements such as dizziness, shakiness, sweatiness, and/or blurred vision.
4. During the previous 7 days, did you make any changes to your medications? If so, please explain them below, including medication name and dosage.

Information text box.

Reminder: If you are having symptoms of hypoglycemia (low blood sugar)--such as rapid heartbeat, shakiness, sweating, dizziness, weakness--or if you think your blood glucose is too low (i.e. under 80 mg/dL):

1. Consume a quick-fix food right away to raise blood glucose such as 3-4 glucose tablets (approximately 15 grams of carbohydrate), 1/2 cup of any non-diet fruit juice or soda, or 1 cup of milk).
2. If you have not already checked your glucose, or are not sure the reading was accurate, check your blood glucose.
3. If your blood glucose is low, recheck blood glucose in 20 minutes after consuming a quick-fix food to make sure it is 80 mg/dL or above. If it's still too low, eat another serving of a quick-fix food.
4. Repeat these steps until the blood glucose level is 80 mg/dL or above. If your next meal is an hour or more away, a snack should be eaten once the quick-fix foods have raised your blood glucose level. The snack should contain some carbohydrate and protein.
5. Please email the study team at atbreakfaststudy@med.umich.edu as soon as possible if you have blood glucose levels below 80 mg/dL or above 300 mg/dL so that they can work with you to adjust your medications if needed. We will be in touch with you within one business day (Monday through Friday, 8 AM- 5PM). Please note that this survey and e-mails are not being reviewed over the weekend or on holidays.
6. Please note that if your blood glucose level is less than 60 mg/dL, you have recurrent low blood sugar, or you could not raise your blood sugar with food, contact your primary care physician urgently.

Reminder about blood pressure: If you are having symptoms of hypotension (low blood pressure)—including lightheadedness, dizziness, or feeling weak—please make sure to stay hydrated and take your blood pressure. If the top number (systolic) is <100 mm Hg, contact your healthcare team immediately. If your systolic blood

pressure is above 180 mmHg and (1) you have symptoms such as chest pain or shortness of breath, you need to go to the emergency room, (2) with mild symptoms such as a headache, contact your healthcare team immediately, or (3) because you haven't taken your blood pressure medications, take your medications and recheck your blood pressure in an hour. For an emergency: Call 911. For immediate assistance, contact your primary care physician or endocrinologist.

Quizzes. As a part of the weekly survey, participants will be asked to complete a short quiz related to the program content delivered that week. The quiz scores will help determine the level of comprehension of the program content, and the need for guidance from the coach.

Text messages. Reminders about targeted behaviors are tied to greater adherence.²⁹ Thus, to encourage adoption and maintenance of the new behaviors, participants will be sent text messages to provide feedback, as well as to motivate, educate, and remind them about targeted behaviors and skills. We will send these automatic, motivational, and educational skill-relevant messages about five times per week.

Mailed materials. Several times throughout the 4 months, the participants may receive mailed materials, including more unusual or hard-to-find foods on their assigned diet like coconut flour and almond flour (for very low-carbohydrate waffles, muffins, pancakes, and bread) and chia seeds (for very low-carbohydrate breakfast parfaits and puddings). We may also send them very low-carbohydrate cookbooks that are lower literacy, budget-friendly, and appropriate for relatively novice cooks. Although meal replacements can be helpful for weight loss,³⁰ this cookbook approach is novel.

Optional question and answer sessions

Monthly online group video sessions with the coach will be offered as an optional way for participants to receive support while they are enrolled in the program. These sessions will be recorded for fidelity purposes and will give participants an opportunity to share and ask questions in a group setting.

Weekly contact during program

week	Email to session materials	Session: Check-in survey	Session: Video and matching handout	Cookbook	Text Messages	Consult with coach (minimum every two weeks or as needed)
1	x (with a second reminder)	x	x	x	x (about 5 times a week)	x
2	x (with a second reminder)	x	x		x (about 5 times a week)	x
3	x (with a second reminder)	x	x		x (about 5 times a week)	x
4	x (with a second reminder)	x	x		x (about 5 times a week)	x
5	x (with a second reminder)	x	x	Optional	x (about 5 times a week)	x
6	x (with a second reminder)	x	x		x (about 5 times a week)	x
7	x (with a second reminder)	x	x		x (about 5 times a week)	x
8	x (with a second reminder)	x	x		x (about 5 times a week)	x
9	x (with a second reminder)	x	x		x (about 5 times a week)	x
10	x (with a second reminder)	x	x	Optional	x (about 5 times a week)	x

11	x (with a second reminder)	x	x		x (about 5 times a week)	x
12	x (with a second reminder)	x	x		x (about 5 times a week)	x
13	x (with a second reminder)	x	x		x (about 5 times a week)	x
14	x (with a second reminder)	x	x		x (about 5 times a week)	x
15	x (with a second reminder)	x	x		x (about 5 times a week)	x
16	x (with a second reminder)	x	x		x (about 5 times a week)	x

Participant retention. To encourage participant retention, participants will be paid up to \$100 for completing the 4-month assessments and will be able to keep any of the intervention-related items we send them (which may include a body weight scale, blood pressure cuff, glucometer, and cookbooks). We include responsive coaching (via phone, video, and/or email) so that participants' questions are answered in a timely way, their comments are replied to supportively, and participants feel taken care of but also accountable. Monthly online group video sessions with the coach will be offered as an optional way for participants to receive support while they are enrolled in the program. We send participants in the program near-daily, unique text messages. Participants have liked these in previous trials, noting they were "very helpful and encouraging," that "they give me occasional reminders that I am not on this journey alone," and were "good reminders to stay focused." We mail participants cookbook gifts, which they have enjoyed, noting that they "helped me to venture outside of my regular ³¹ menu," they were "very inspiring and made trying new things possible," and "OMGoodness these help soooooo much!" This trial will build on our experience of effectively recruiting and retaining similar participants. Our 4-month pilot trial retained 81% of participants.

Participants may be offered the option to complete an optional Long-Term survey at least 6 months after completion of the study. The survey will provide information regarding participants' health, diet, etc. after completing the study. Participants who complete the survey will receive a \$20 Amazon gift card.

Outcomes.

Outcomes Table

	Blood tests	CGM (over 2 weeks)	Self-report survey	Blood pressure (several times over 2 weeks)	1-2 24-hour dietary recall	Body weight
Baseline	x	optional	x	x	x	x
Outcome (16 weeks later)	x	optional	x	x	x	x

Participants who are unable to return to Labcorp for 4 month blood draws may be performing an at-home finger prick using a lancet and very small collection tube. They may be asked to prick their finger, collect a small amount of blood in a tiny tube, called a capillary tube, and then mail this back to the lab. The risks of pricking yourself for the at-home test kit include temporary discomfort from the stick, localized bleeding, or localized infection. This test is performed by DTI Laboratories, who is not affiliated with the University of Michigan or Michigan Medicine. These blood tests will measure their hemoglobin A1c (HbA1c).

Aim 1: Assess acceptability and feasibility.

Acceptability: Intervention satisfaction. At month 4, we will ask participants, "How would you rate your overall satisfaction with the program?" on a 1-6 Likert scale (1=not at all satisfied; 6=very satisfied). We have denoted mean ratings of 5.0 on the 1-6 satisfaction scale our *a priori* benchmark for acceptability. Based on the

satisfaction rating from our most recent two trials of adults using our 16-week program (mean=6.0, SD=1.3; mean 6.4, SD=0.7), using the conservative values of a mean of 6.0 and SD of 1.3, this trial has >90% power to detect this level of satisfaction (vs a mean of 5.0) using a two-tailed *t*-test at an alpha level of 5%.

Other exploratory outcomes for acceptability:

Health-related quality of life. This is a central aspect of wellbeing. At baseline and 4 months later we will use the PROMIS 29,³³ a psychometrically sound, clinically relevant measure.^{34,35} It assesses seven domains: physical functioning, anxiety, depression, fatigue, sleep disturbance, social functioning, and pain. We will explore how responses changed from the baseline to the end of the study by using a two-tailed paired *t*-test, with a significance level of 0.05.

Physical symptoms. We will monitor for symptoms throughout the trial. At baseline and 4 months later we will also measure physical symptoms using a short, face-valid measure of physical symptoms.³⁶ Participants report how often over the past month they have had symptoms such as dizziness, diarrhea, constipation, headaches, blurred vision, nausea, pain in their hands or feet, heartburn, and acne. We will also capture spontaneously reported adverse events with weekly open-ended prompts and report the incidence of adverse events, including the percentages of participants who experienced treatment-emergent adverse events of particular significance. We will explore how symptoms changed from the baseline to the end of the study by using a two-tailed paired *t*-test, with a significance level of 0.05.

Exploratory open-ended survey questions and qualitative interviews. In the 4-month survey, all participants will be asked open-ended questions about the aspects of the program participants enjoyed, which aspects could be improved, what made it easier to stick with the program, and which factors made adherence more difficult.

We will conduct qualitative semi-structured interviews with 30 participants at the end of the trial, chosen to have a diverse range of responses about the program based on their open-ended survey responses. We will conduct qualitative interviews to better understand the strengths, weaknesses, and barriers of our intervention, so that we can inform future testing of our interventions in clinical and research settings. This will allow us to explore the experience of the participants in greater depth, including their perceptions of the intervention, as well as barriers to and facilitators of their ability to make long-lasting dietary changes. Dr. Saslow (PI) has overseen qualitative research and data analysis for several previous dietary trials and will lead analysis of the interviews. We will model the interview guide and data analysis on prior research, using a semi-structured interview guide that we have implemented in three previous trials, which includes open-ended questions to encourage participants' perspectives, thoughts, and beliefs about the intervention and its components. Participants will be interviewed by non-intervention staff from our research team. Based on our experience during previous trials, these interviews will last approximately 20-30 minutes. Two coders will independently categorize responses from the interviews into broad themes. These themes will then be iteratively refined until consensus has been reached between the coders, typically taking about 2-3 rounds of coding and discussion. Then, coders will code the transcripts independently. Finally, they will create a summary of the qualitative data, with evidence from participant quotes,³⁷ which should be able to inform future trials of the intervention.

Feasibility: Completed sessions. For feasibility, we will record the mean number of completed sessions (out of 16 possible). We have denoted a 60% attendance of assigned sessions as our *a priori* benchmark for feasibility. Based on the completion rates from our most recent two trials of adults using our program (mean=73.9%, SD=28.9%; mean=79.3%, SD=32.4%) and using a SD of 30%, this trial has > 85% power to detect this level of completion (vs 60% completion) using a two-tailed *t*-test at an alpha level of 5%.

Other exploratory outcomes for feasibility.

Participant recruitment and progress through the trial. As recommended by the Consolidated Standards of Reporting Trials (CONSORT) guidelines,³⁸ we will report on the percentage enrolled from each recruitment method, the number excluded and why, the number who chose not to enter the trial and why, and the number and reasons for withdrawal.

Dietary adherence. We will assess dietary adherence with 1-2 unannounced 24-hour dietary recalls at baseline and two at 4 months conducted by a dietitian. At month 4, this will serve as a check on our intervention fidelity in terms of whether we have achieved our targeted macronutrient levels for breakfasts. We will explore what percentage of calories in participants breakfasts were derived from carbohydrates, in addition to exploring what percentage of participants ate breakfasts that had 20% or less of their calories from carbohydrates. We will also examine the macronutrient content and quality of other eating occasions throughout the day to assess whether breakfast quality impacted the subsequent diet.

Aim 2: Assess changes in health and psychological outcomes. As appropriate, for the following measures, we will explore how each of these outcomes changed from the baseline to the end of the study by using a two-tailed paired *t*-test, with a significance level of 0.05.

HbA1c. *Rationale:* HbA1c is the most widely accepted measure of overall glycemic control in the clinical care of type 2 diabetes and is a strong predictor of the risk of microvascular complications from diabetes.³⁹ *Methods:* HbA1c levels will be measured by standard immunoturbidimetric assay methods and quality control measures at a Clinical Laboratory Improvement Amendments (CLIA) certified lab (i.e., LabCorp).

Anti-hyperglycemic medications. *Rationale:* Sulfonylureas and insulin increase the risk of hypoglycemia, which is linked to higher mortality and lower quality of life in diabetes, and these medications can cause weight gain.⁴⁰ *Methods:* We will ask participants about their current diabetes-related medication regimen using questions we have employed in prior studies.¹⁸ We will measure the intensity of the treatment using a medication-effect score, which assesses the overall intensity of an anti-hyperglycemic medication regimen by combining dosage and strength of medications.⁴¹

Diabetes control. *Rationale:* Diabetes remission has been defined as lowering HbA1c to below 6.5% without the use of anti-hyperglycemic medications other than metformin.⁴² *Methods:* We will explore metrics of diabetes control and report on the percentage of participants who (a) lower HbA1c to below 7.0% without increasing their medication effect score, (b) lower their HbA1c to below 6.5% without increasing their medication effect score, and (c) lower their HbA1c to below 6.5%, without increasing their medication effect score, and take no anti-hyperglycemic medications other than metformin.

Glycemic variability. *Rationale:* Compared to people with normal glucose tolerance, people with prediabetes and type 2 diabetes have greater intraday glycemic variability.⁴³ Glycemic variability is thought to lead to complications by increased oxidative stress and vascular endothelial damage.⁴⁴ In people with type 2 diabetes, glycemic variability has been tied to a higher risk of renal disease, macrovascular events, ulceration/gangrene, cardiovascular disease, and mortality.⁴⁵ Furthermore, low-carbohydrate diets are related to lower glycemic variability in people with type 1 diabetes^{46,47} and type 2 diabetes,⁸ and carbohydrate intake is the strongest factor impacting post-prandial glycemia.⁴⁸ *Methods:* At baseline and 4 months, we may place an Abbott Libre Pro continuous glucose monitoring device on a patient's upper arm or mail it to them to self-administer the device. Participants with this type of sensor receive no feedback, as the sensor is blinded. All sensors will be placed using an alcohol pad to clean the skin and Skin-tac wipe to ensure the sensor stays in place. These continuous glucose monitors are FDA-approved and require no calibration. They record participants' glucose levels in the interstitial fluid by a glucose oxidase method every 15 minutes, continuously for 14 days at each time point (0 and 4 months). The research team would then download sensor data at the end of the measurement period. Following previous research, we will assess the glucose variability and the proportion of time spent in the euglycemic (3-7.8 mmol/l) and hyperglycemic (≥ 11.1 mmol/l) states, following previous standards for interstitial glucose concentrations.⁴⁹⁻⁵¹

Body weight. *Rationale:* Weight loss, even in modest amounts, predicts improved glycemic control in type 2 diabetes.⁵² *Methods:* We may give participants a body weight scale and ask participants to weigh themselves weekly, in order to help tailor coaching support, but weight change from baseline to 4 months will be our outcome of interest. We may also measure their body weight in person at baseline and 4 months, at the same time that we also measure associated aspects of waist and hip circumference. We will examine average weight loss and the percentage of participants who lose 5%, a clinically meaningful amount of weight loss.

Lipids. *Rationale:* Elevated triglyceride levels⁵³ and elevated low-density lipoprotein (LDL) cholesterol and reduced high-density lipoprotein (HDL) cholesterol⁵⁴ have been associated with increased cardiovascular disease. In clinical trials of low-carbohydrate diets, triglycerides decrease and HDL increases, while LDL cholesterol has more mixed results:⁵⁵ some trials show increased LDL-C levels,⁵⁶ though other data suggest that these increases may normalize over time (i.e., 15 months).⁵⁷ Small particle LDL (sLDL) is particularly associated with cardiovascular risk and is often reduced by low-carbohydrate diets.⁵⁵ *Methods:* At baseline and 4 months later, we will measure triglycerides and fractionated cholesterol using LabCorp's Nuclear magnetic resonance (NMR) LipoProfile.⁵⁸ This advanced lipid assay provides measures that are more tightly tied to elevated cardiovascular risk than conventional lipid assays.⁵⁹

Insulin resistance. *Rationale:* As part of the progression of prediabetes developing into type 2 diabetes, insulin resistance followed by altered insulin secretion occurs.⁶⁰ Research suggests that when glucose is lowered, as with a reduced-carbohydrate diet, insulin resistance may also improve.⁶¹ *Methods:* At baseline and 4 months, we will use fasting insulin and glucose to estimate insulin resistance by calculating Homeostatic

Model Assessment-Insulin Resistance (HOMA-IR). HOMA-IR is a widely used method of estimating insulin resistance using a single fasting blood draw that has been reported in over 500 studies and correlates well with results from a hyperinsulinemic-euglycemic clamp.⁶²

Inflammation. We may assess C-reactive protein at baseline and outcome.

Blood pressure. *Rationale:* Adults with type 2 diabetes are at higher risk of cardiovascular disease, especially if they also have hypertension.⁶³ A low-carbohydrate diet may reduce blood pressure through weight loss and its impact on insulin (which alters renal sodium transport and leads to diuresis).⁶⁴⁻⁶⁶ A meta-analysis found that low-carbohydrate diets reduce systolic blood pressure by ~5 mmHg.⁶⁷ *Methods:* We may give participants a blood pressure cuff. Given the white-coat effect, in which in-office blood pressure can be quite elevated as compared to home-measured blood pressure,⁶⁸ we will use a home-based measurement. We may ask participants to measure their blood pressure several times a week for the first and last two weeks of the intervention, using the average over those 2-week periods as our assessment of interest, with change from baseline to 4 months being our outcome of interest. "Self-reported blood pressure survey. Welcome! Please only enter what you measured today. Blood pressure, mmHg: Systolic blood pressure (top number), Diastolic blood pressure (bottom number)." Participants will also be asked to check their blood pressure if they have symptoms of hypotension.

Self-efficacy for dietary adherence. *Rationale:* Social cognitive theory is one of the most commonly applied health behavior change theories. One of its central concepts is perceived self-efficacy, the confidence in one's ability to perform a behavior that will result in an expected outcome. Greater self-efficacy is thought to increase the effort people will put into accomplishing their goals.²⁴ Diet-following self-efficacy has been predictive of dietary adherence,⁶⁹ and in a previous weight management intervention was a mediator of weight loss.⁷⁰ *Methods:* At baseline and 4 months later we will measure this with the 8-item Weight Efficacy Lifestyle Questionnaire Short-Form (WEL-SF), which assesses self-efficacy for dietary adherence when facing a variety of challenging situations, including poor mood and social situations.⁷¹

Satiety and food responsiveness. *Rationale:* According to the externality theory of obesity, adults with obesity are less responsive to internal satiety cues and more responsive to external food cues.⁷² *Methods:* At baseline and 4 months later, we will assess whether the intervention improves these two factors using two 4-item subscales of the Adult Eating Behavior Questionnaire, one for each factor.⁷³

Aim 3: Assess factors that identify individuals who will particularly benefit from the intervention.

These moderation analyses will contribute to a nascent research approach for personalized nutrition, which responds to Objective 2-5 of the NIH's May 2020 Strategic Plan for NIH Nutrition Research. To characterize the heterogeneity of intervention effects among participants for change in HbA1c, we will regress change in the outcome as a function of the following potential moderating variables. A statistically significant moderator would indicate the need for further investigation of that variable's role.

Sex. *Rationale:* Emerging research shows that men may lose more weight than women while following a very low-carbohydrate diet.^{74,75} *Methods:* We will explore whether men have greater reduction in HbA1c, using an indicator variable.

Literacy level. *Rationale:* Adults with lower health literacy levels can have poorer diabetes control.^{4,5} We will explore whether baseline health literacy moderates the impact of the intervention on change in HbA1c. *Methods:* We will measure health literacy with a 4-item health literacy screening tool, known as the BRIEF.⁷⁶

Emotional eating. *Rationale:* Emotional eating predicts weight gain and increases the challenge of losing weight.^{77,78} We will explore whether baseline emotional eating moderates the impact of the intervention on change in HbA1c. *Methods:* At baseline and 4 months later, we will measure emotional eating with the 4-item coping subscale of the Palatable Eating Motives Scale (PEMS), which asks people to consider what reasons people give for eating highly palatable foods, such as sweets, salty snacks, fast foods, and sugary drinks, with prompts including "to cheer up when you are in a bad mood" and "to forget about your problems."⁷⁹

Food addiction. *Rationale:* Food addiction can be a barrier for dietary adherence. *Methods:* At baseline and 4 months later, we will measure emotional eating with the 13-item Yale Food Addiction Scale 2.⁸⁰

Insulin resistance. *Rationale:* Some previous research has found that insulin-resistant adults lose more weight when assigned to a lower versus higher carbohydrate diet, although results are mixed.⁸¹⁻⁸⁵ *Methods:* We will explore whether baseline insulin resistance moderates the impact of the intervention on change in HbA1c.

Potential pitfalls.

Recruitment. If enrollment lags significantly behind the original target, additional contingency plans include (1) contacting individuals directly via phone or email 2 weeks after the initial invitation letter is sent; (2) accepting direct referrals to the program from healthcare providers; (3) using flyers and advertising on a variety of other institutional websites, including the UMHealthResearch site; (4) using targeted ads on Google, YouTube, and social media websites; or (5) outreach to additional affiliated medical centers. We have effectively used these strategies before in similar populations. LabCorp has thousands of locations across the United States, allowing us to recruit nationally, if need be. Along with the possibility of a home application of the continuous glucose monitor as a secondary health outcome, glycemic variability.

Safety. We are aware that hypoglycemia is an important danger in this population, which can occur when dietary changes occur, as participants may become overmedicated. To guard against this, we have a several-pronged approach. (1) An intake session. All participants will have an intake session via a video chat or phone call with the study MD to discuss any initial medication changes. For example, if a participant is on short-acting insulin for breakfast, they would need to stop that from the start of the trial. If a participant is on glipizide in the morning, then that pill might be stopped, reduced, or delayed until lunch. (2) Self-care education. All participants will be taught about strategies they can use to mitigate dangerously low blood glucose levels, which is standard advice for our previous trials of a very low-carbohydrate diet in similar patients. They will be told about what measurements warrant self-care and what is an emergency. (3) Self-monitoring. Participants taking insulin or other hypoglycemic agents will be asked to check their blood glucose before each injection (a standard-of-care approach) and both fasting and pre-dinner. If the majority of blood glucose values drop below 110 mg/dL, or there are other concerning blood glucose patterns, we will reduce or stop medications, as described in the protection of human subjects section. Participants will share their blood glucose levels with our study, via a weekly mobile-friendly survey (see the weekly check-in survey described above for more information). This will allow us to carefully monitor participants' blood glucose levels. Blood pressure will be measured several times a week at the start and end of the trial.

(4) Regular monitoring by study team. All information about participant blood glucose levels and/or symptoms of hypoglycemia will be collected and relayed in our study dashboard, accessible to our study staff, including Dr. Sarah Kim. Dr. Kim has more than a decade of experience not only managing medications for adults with poorly controlled type 2 diabetes but also for such patients making carbohydrate-lowering changes to their diet. We will follow published protocols of how medications should be managed in these situations.⁸⁶ This combination of an intake session, self-care, self-monitoring, and educated oversight should enable us to keep participants safe.

Moreover, although we do not intend for participants to follow a very low-carbohydrate diet for all of their meals, if they do, it may cause nutritional ketosis, which is a fundamentally different process than diabetic ketoacidosis, a dangerous condition that may occur in patients with type 1 diabetes, and sometimes in those with type 2 diabetes. Nutritional ketosis is a biochemically regulated process that results in the production of ketone bodies from fatty acids during periods of fasting or carbohydrate reduction. During nutritional ketosis, blood ketone levels are 0.5-3 mM in the presence of normal blood glucose.⁸⁷ And, in one study, blood pH was no lower than 7.37 in individuals following such a diet.⁸⁸ In contrast, in diabetic ketoacidosis, ketone production is unregulated, with blood ketone levels surpassing 25 mM and blood glucose levels are high (>250 mg/dL). Nutritional ketosis is typically well-tolerated and side effects, such as constipation and muscle cramps, can be treated with hydration and other self-care. In addition, participants report reduced hunger⁸⁹ and positive health changes, such as improvements in signs and/or symptoms related to type 2 diabetes,⁹⁰ migraines,⁹¹ irritable bowel syndrome,⁹² heartburn,⁹³ nonalcoholic fatty liver disease,⁹⁴ and pain.⁹⁵

As we have done in previous trials, all participants in the trial will consent to allow us to communicate with their primary care provider. We will only allow participants to join the trial if their physicians approve their participation in the trial, the physicians approve that we can make medication adjustments as needed for participant safety, and the physicians have a way for us to communicate with them, such as (1) being in the Michigan Medical system so that we could directly message them, (2) having a fax number, so that we can send them HIPAA-compliant faxes, (3) having a direct email, so that we can send them secure messages through the Michigan Medicine secure email system, or (4) having a phone number where we could leave a private message.

The participant's personal physician will receive information about the study before a participant begins the study. The letter will include information about medication changes that are likely to occur and participant

monitoring plans. We will describe that our study physician, an endocrinologist, will be making medication adjustments over the course of the 4-month trial, and the letter will describe the general approach that will be taken to do so. Whenever the study physician makes any medication adjustment recommendations, the study will notify the participant's personal physician in a timely manner, within 1 business day, by sending a high priority message through the secure messaging system as part of our medical system, which can be made by our UM study team, where possible, plus any additional way that the physician prefers to be contacted (such as email, phone call, fax, etc.). The notification will describe the reason why the medication was adjusted. Moreover, the participant's personal physician can reach out to study staff, and therefore the study physician, as needed for discussion about these changes.

We will contact the primary care providers within 1 business day of being aware of a serious adverse event or a change in medication. How this will be documented in the participants' medical record is up to the providers, as during the trial we are not going to be directly accessing the participants' medical records ourselves. (We will only use medical records for recruitment purposes.)

To avert the risk of hypoglycemia, we will put several other measures into place:

- The study physician may adjust hypoglycemic agents at the start of the trial, to reduce the risk of hypoglycemia.
- We will require participants to measure their blood glucose levels using the standard of care. Therefore, if they are on hypoglycemic agents with a risk of hypoglycemia such as insulin or a secretagogue, they will be asked to measure their blood glucose levels regularly. Then, the timing of the measurements will depend on the particular type of medication. Participants taking insulin or other hypoglycemia agents, and therefore at a higher risk for hypoglycemia may be asked to check their blood glucose before each injection (a standard-of-care approach), and both fasting and pre-dinner, depending on the timing of their particular medications.
- We will provide hypoglycemia instructions to all participants in the beginning of trial with confirmation that the patient knows how to treat hypoglycemia. These instructions will state that for low blood glucose levels (below 80 mg/dl), participants should consume 15 g of fast acting carbohydrate and recheck their blood glucose levels in 15 minutes, repeating until their blood glucose reaches >100 mg/dl) and that the participants will have a prescription for glucagon if on a hypoglycemic agent such as insulin or a secretagogue.
- We will ensure that participants are able to reach out to their personal physician with any emergent issues. They can contact the study staff for a response from our study physician by the next working day, as appropriate.
- We will ask the participants to report to study staff immediately any blood glucose values < 80 mg/dl or > 300 mg/dl. Otherwise, participants are asked to report on their blood glucose levels in the weekly check-in survey; we ask participants to report their highest and lowest blood sugar levels of the week for when they were fasting and non-fasting (such as just before dinner). If participants are supposed to be measuring their blood glucose levels but do not report them for the week, we will send them reminder emails, their coach will mention it in the one-on-one meetings, and/or we will call or text participants. To provide incentive for completing the weekly check-in surveys and reporting blood glucose levels, a \$4 amount will be awarded per completed survey, added to their \$36 final gift card after completing the program, for a total of up to \$100.

Eligibility Criteria

Inclusion Criteria:

- HbA1c 7% or higher
- 18-80 years old
- The ability to understand verbal and written English
- Willingness to follow the prescribed diet
- Able to consent and follow directions
- Willingness to regularly check blood glucose levels as required

Exclusion Criteria:

- Inability to provide informed consent
- Pregnant, breastfeeding, or planning for either in the next 6 months or <6 months postpartum

- Low C-peptide and possible subsequent GAD 65 level that suggests type 1 diabetes, clinical factors that suggest type 1 diabetes (lean, lack of family history, and diabetic ketoacidosis in the past) or a previous diagnosis of type 1 diabetes or latent autoimmune diabetes
- Triglycerides are greater than 999mg/dL on the screening blood draw
- Cancer, heart failure, or kidney failure
- Vegan
- Untreated mental health condition
- Currently following a very low-carbohydrate diet or breakfasts
 - Thyroid levels out of range
- Alcoholism
- Previous bariatric surgery
- Difficulty chewing or swallowing
- Dependence on others for food preparation
- Currently enrolled in another investigative study that might conflict with this research

Age Limits Minimum Age: 18 years **Maximum Age:** 80

Enrollment – Planned:

up to 120 participants

5% Asian

15% Black

55% White and not Hispanic

22% White and Hispanic

3% Other

53% male, 47% female

4.3. Outcome Measures

Name: Ratings of intervention satisfaction

Type: Primary

Time Frame: 4 months

Brief Description: To assess acceptability, at 4 months we will ask participants, “How would you rate your overall satisfaction with the program?” on a Likert scale from 1 (*very dissatisfied*) to 6 (*very satisfied*).

Name: Quality of life

Type: Other

Time Frame: Baseline and Month 4

Brief Description: 29-item Patient-Reported Outcomes Measurement Information System (PROMIS) short-form measure of quality of life including physical function, anxiety, depressive symptoms, fatigue, sleep disturbance, ability to participate in social roles and activities, pain interference, and pain intensity.

Name: Physical symptoms

Type: Other

Time Frame: Baseline and Month 4

Brief Description: Participants report how often over the past month they have had symptoms such as dizziness, diarrhea, constipation, headaches, blurred vision, nausea, pain in their hands or feet, heartburn, and acne.

Name: Exploratory open-ended survey questions and qualitative interviews

Type: Other

Time Frame: Month 4

Brief Description: Participants will be asked open-ended questions about the aspects of the program participants enjoyed, which aspects could be improved, what made it easier to stick with the program, and

which factors made adherence more difficult. We will conduct qualitative semi-structured interviews with a subset of participants to better understand the strengths, weaknesses, and barriers of our intervention.

Name: Assessment of program feasibility

Type: Primary

Time Frame: 4 months

Brief Description: For feasibility, we will record the mean number of completed sessions (out of 16 possible). We have denoted a 60% attendance of assigned sessions as our a priori benchmark for feasibility.

Name: Dietary adherence

Type: Other

Time Frame: Baseline and Month 4

Brief Description: Dietary macronutrients and calories measured with 1-2 unannounced 24-food recalls at each time period.

Name: Glycated hemoglobin

Type: Other

Time Frame: Baseline and Month 4

Brief Description: Blood measurement which represents average glycemic control and conversion to type 2 diabetes if at or above the 6.5% threshold.

Name: Medications

Type: Other

Time Frame: Throughout program

Brief Description: Number and types of medications

Name: Glycemic variability

Type: Other

Time Frame: Baseline and Month 4

Brief Description: Glycemic variability, as measured by a continuous glucose monitor

Name: Body weight

Type: Other

Time Frame: Baseline and Month 4

Brief Description: Body weight measured with a scale

Name: Lipids

Type: Other

Time Frame: Baseline and Month 4

Brief Description: Lipids include LDL (low-density lipoprotein cholesterol), HDL (high-density lipoprotein cholesterol), triglycerides, and results from the nuclear magnetic resonance LipoProfile.

Name: Insulin resistance

Type: Other

Time Frame: Baseline and Month 4

Brief Description: Homeostatic Model Assessment-Insulin Resistance, calculated with fasting insulin and glucose

Name: Blood pressure

Type: Other

Time Frame: Baseline and Month 4

Brief Description: Systolic and diastolic blood pressure

Name: Self-efficacy for dietary adherence

Type: Other

Time Frame: Baseline and Month 4

Brief Description: We will use the 8-item Weight Efficacy Lifestyle Questionnaire Short-Form (WEL-SF) to assess dietary adherence when facing a variety of challenging situations including poor mood and social situations.

Name: Satiety and food responsiveness

Type: Other

Time Frame: Baseline and Month 4

Brief Description: We will assess whether the intervention improves these two factors using two 4-item subscales of the Adult Eating Behavior Questionnaire, one for responsiveness to internal satiety cues and one for responsiveness to external food cues.

Name: Health literacy

Type: Other

Time Frame: Baseline

Brief Description: We will measure health literacy with a 4-Item health literacy screening tool, known as the BRIEF.

Name: Emotional eating

Type: Other

Time Frame: Baseline and Month 4

Brief Description: We will measure emotional eating with the coping subscale of the Palatable Eating Motives Scale (PEMS), which asks people to consider what reasons people give for eating highly palatable foods such as sweets, salty snacks, fast foods, and sugary drinks, with prompts including “to cheer up when you are in a bad mood” and “to forget about your problems.”

Name: Food addiction

Type: Other

Time Frame: Baseline and Month 4

Brief Description: We will measure food addiction with the Yale Food Addiction Scale 2, which asks people to consider any problematic craving and overeating related to food.

RECRUITMENT AND RETENTION PLAN

Recruitment plan

Testing of several different methods has allowed us to identify an effective recruitment approach. First, we will search medical records of Michigan Medicine for potentially eligible participants. An initial search identified >120,000 adults in our system likely to be eligible based on age, HbA1c in the past year, and diagnoses.

As we have done in previous research, each year of the study, we will initially contact the pool of potentially eligible participants by sending them a letter and flyer using a HIPAA-compliant company describing the study, which will refer them to a study web page and initial online screening questionnaire. All recruitment materials will be written at no higher than a fifth-grade reading level. We may follow up with a phone call. Participants that meet inclusion, and not any of the exclusion criteria, and consent to participate, will be asked to follow through with baseline activities, including the following, after which eligible participants will be assigned to the intervention:

- Fill out baseline surveys.
- Watch a video describing the study, as well as answer questions about their goals for participation and pros and cons of participation, which previous researchers have used to reduce dropout by ensuring all participants are ready to make the changes that we will require in the trial.
- Participate in 1-2 24-hour food recalls by phone.
- Get a fasting blood draw.
- May attend an online appointment to have a continuous glucose monitor (CGM) attached for 14 days..

In previous research, this approach has been highly effective: more than 10% of patients that we mail a letter to then fill out our baseline screening survey (a high response rate in the world of clinical trials). Considering the large number of participants with poorly controlled type 2 diabetes in our medical system, this approach should yield a more-than-sufficient supply of eligible participants.

However, if we find that any gender or racial/ethnic group is joining our study in an unrepresentative way (a much greater or smaller percentage than expected), we can alter who we target, contact, and/or include in the trials. We can contact potentially eligible participants, from particular demographics, based on medical records, which are tied to a large medical network. We can use social media, such as Facebook and Instagram, to target ads to particular demographics, as well as working with the recruitment support program at UM's Michigan Institute for Clinical and Health Research (MICHHR), to help recruit appropriate participants.

Moreover, if enrollment lags significantly behind the original target, additional contingency plans include (1) contacting individuals directly via phone or email 2 weeks after the initial invitation letter is sent; (2) accepting direct referrals to the program from healthcare providers; (3) using flyers and advertising on a variety of other institutional websites, including the UMHealthResearch site; (4) using paid advertisements, including targeted ads on Google, YouTube, research engagement platforms, such as Altura Studies and Policy Lab and social media websites such as Facebook; or (5) outreach to additional medical centers.

Retention plan

To encourage retention, we include a variety of supports and incentives including:

- Participants are paid up to \$100 at 4 months for their study-related measurements and their results are provided for free. They are incentivized monetarily to complete the weekly survey for 16 weeks. A \$4 amount will be awarded per completed survey, added to their \$36 final gift card after completing the program, for a total of up to \$100.
- We include responsive coaching so that participants' questions are answered in a timely way, their comments are replied to supportively, and participants feel taken care of but also accountable.
- We send participants in the program near-daily, unique text messages. Participants have liked these in previous trials, noting they were "very helpful and encouraging," that "they give me occasional reminders that I am not on this journey alone," and were "good reminders to stay focused."
- We mail participants cookbook gifts, which they have enjoyed, noting that they "helped me to venture outside of my regular ³¹ menu," they were "very inspiring and made trying new things possible," and "OMGoodness these help soooooo much!"

This trial will build on our experience of effectively recruiting and retaining similar participants.

PROTECTION OF HUMAN SUBJECTS

Risks to the subjects

Sources of materials

Questionnaires and blood specimens will be obtained only after informed consent. All materials and data collected from participants will be used for research purposes only. Sources of materials include responses to the self-report questionnaire and results of laboratory testing of blood specimens.

Potential risks

Very low-carbohydrate breakfast: Based on dietary adherence to a full-day very low-carbohydrate diet, several minor adverse effects may occur including constipation, muscle cramps, elevated LDL cholesterol, diarrhea, general weakness, and rash. Most of these occur at diet initiation, are short-lived, and are generally alleviated by adequate fluid intake and other minor dietary modifications that will be addressed in the intervention.

Other theoretical risks of the reduced-carbohydrate diet include nephrolithiasis (kidney stones) and increased bone turnover. The potential for these side effects is derived from pathophysiologic theory, studies of the diet using intermediate endpoints, and extrapolation from similar diet approaches, such as the ketogenic diet for epilepsy.

Hypoglycemia: A reduced-carbohydrate diet may lead to decreases in glucose levels. In persons receiving

medications such as sulfonylureas or insulin, this could increase the risk of hypoglycemia if appropriate medication adjustments are not made. Study physicians will oversee changes in medications, specifically reductions (or discontinuations if at a low dose), in an order that typically prioritizes reductions/discontinuations as follows: (1) insulin, (2) sulfonylureas, (3) meglitinides (secretagogues), (4) SGLT-2 inhibitors, (5) GLP-1 agonists, GLP-1/GIP dual agonists, and DPP4 inhibitors, (6) alpha glucosidase inhibitors, (7) thiazolidinediones (TZD).

Biguanides (e.g., metformin) are typically continued unless glycated hemoglobin levels (HbA_{1c}) are consistently below 6.5%. Overall, medications that do not have an increased risk of hypoglycemia (GLP-1 agonists, GLP-1/GIP dual agonist, DPP-4 inhibitors, SGLT-2 inhibitors, alpha glucosidase inhibitors (taken before carbohydrate containing meal), thiazolidinediones, and metformin) are not usually adjusted, unless the participant is having adverse reactions specific to that medication.

Initial medication adjustments typically involve reducing a medication dose by up to one-half, and are aimed at preventing hypoglycemia when initiating carbohydrate restriction. The number of medications reduced is calibrated based on initial HbA_{1c} levels, current medications taken, and their current eating pattern, with limited medication reductions in participants with high HbA_{1c} levels and more extensive reductions in persons with HbA_{1c} levels in the low diabetic range. The table below has some suggested medication reductions; these reductions are examples that need to be individualized.

Initial HbA _{1c}	Suggested initial medication reduction
9-12%	- Continue Metformin, TZD (thiazolidinedione), secretagogue, basal insulin, GLP-1 (glucagon-like peptide 1) agonists or GIP dual agonists, DPP-4 (dipeptidyl peptidase 4) inhibitors, and SGLT-2 inhibitors - Stop: Acarbose, short-acting insulin
7-9%	- Continue Metformin, TZD (thiazolidinedione), GLP-1 (glucagon-like peptide 1) agonists, GLP-1/GIP dual agonists, DPP-4 (dipeptidyl peptidase 4) inhibitors, and SGLT-2 inhibitors - Reduce by 0-50%: secretagogues, intermediate and long-acting insulin - Stop: Acarbose, short-acting insulin

Medication adjustments are made based off of the participants' self-reported blood glucose readings and are altered on a case-by-case basis.

- If a blood glucose level is above 110 mg/dL, no medications will be adjusted.
- If a blood glucose level is between 90-110 mg/dL, we will ask participants to continue to monitor their blood glucose per individual frequency and if their blood glucose is again between 90-110 mg/dL, we will down titrate their blood glucose medications.
- If a blood glucose level is below 90 mg/dL, we will down titrate their blood glucose medications.

Medications are adjusted in the following manor:

- Long-acting insulin is reduced by 10-20% (or more, based on blood glucose readings).
- The pre-prandial dose of rapid- or short-acting insulin is reduced by 10-20% (or more, based on blood glucose readings).
- For sulfonylureas, if the medication is taken once daily, we will decrease the dosage by 50%.
- For sulfonylureas, if the medication is taken twice daily, we will decrease or discontinue one of the doses. If the low blood sugar level occurred pre dinner, we will decrease or discontinue the morning dose. If the low blood sugar level occurred when fasted, we will decrease or discontinue the evening dose or morning dose, depending on the type of sulfonylurea the patient is taking.

We are aware that hypoglycemia is an important danger in this population, which can occur when dietary changes occur, as participants may become overmedicated. To guard against this, we have a several-pronged approach. (1) An intake session. All participants will have an intake session via a video chat or phone call with the study MD to discuss any initial medication changes. For example, if a participant is on short-acting insulin for breakfast, they would need to stop that from the start of the trial. If a participant is on glipizide in the morning, then that pill might be stopped, reduced, or delayed until lunch. (2) Self-care education. All

participants will be taught about strategies they can use to mitigate dangerously low blood glucose levels, which is standard advice for our previous trials of a very low-carbohydrate diet in similar patients. They will be told about what measurements warrant self-care and what is an emergency. (3) Self-monitoring. Participants taking insulin or other hypoglycemic agents like secretagogues, and therefore at a higher risk for hypoglycemia will be asked to check their blood glucose before each injection (a standard-of-care approach), and both fasting and pre-dinner, depending on the timing of their particular medications. If the majority of blood glucose values drop below 110 mg/dL, or there are other concerning blood glucose patterns, we will reduce or stop medications, as described in the “Protection of Human Subjects” section. Participants will share their blood glucose levels with our study, via a mobile-friendly survey. This will allow us to carefully monitor participants’ blood glucose levels. (4) Regularly monitoring by study team. All information about participant blood glucose levels and/or symptoms of hypoglycemia will be collected and relayed in our study dashboard, accessible to our study staff, including Dr. Sarah Kim. Dr. Kim has more than a decade of experience not only managing medications for adults with poorly controlled type 2 diabetes but also for such patients making carbohydrate-lowering changes to their diet. We will follow published protocols of how medications should be managed in these situations.⁸⁶ This combination of an intake session, self-care, self-monitoring, and educated oversight should enable us to keep participants safe.

The study MD will review these medication adjustments as well as any symptoms reported by participants using information collected from participants on a weekly basis during the 4-month trial, and she will communicate suggested changes in anti-hyperglycemic medications to participants. Study participants will be able to contact study staff using a study phone number for questions or problems, and staff will be able to reach study physicians by pager or cell phone for more urgent problems. Primary care physicians for participants will receive information about the study before a participant begins the study. The study MD will help to make sure that primary care physicians are informed of any suggested changes to medication regimens and will consult with primary care physicians where indicated.

Hypotension: Reductions in blood pressure and also weight loss have been reported with this way of eating. We will ask participants to report symptoms consistent with orthostatic hypotension. Participants with possible symptoms consistent with low blood pressure will be referred to see their primary care physician, and if need be, consult with the physicians on our study team.

Venipuncture: There is a small risk that the venipuncture associated with the blood draws and the continuous glucose monitor may cause bruising or infection. Rarely, presyncope or syncope can occur.

Questionnaires and interviews: These carry a minimal risk for emotional discomfort and stress, although we will ask about emotional functioning, including 4 items about depressive symptoms and 4 items about anxiety.

Potential benefits of the proposed research to subjects and others

Participants will a) receive the intervention free of charge, and b) may improve their health.

Importance of the knowledge to be gained

This study may benefit society overall by significantly improving our ability to treat type 2 diabetes.

Adequacy of protection against risks

Recruitment and informed consent

Potential participants will be asked to answer a short online self-report questionnaire to perform a preliminary assessment of eligibility, after consenting to be screened in the same survey. Participants who appear eligible based on this screening survey will be asked to review the full study consent form. They will meet with the study team virtually or over the phone to discuss the consent before signing the form online.

Protection against risk

All measures for protection against risks will be applied. Participants will be told that their participation is voluntary and that they can choose to withdraw from the study at any time without any further obligation.

Privacy and confidentiality: Participants will be assigned unique, coded, confidential identifiers (code numbers), which will be used to label all data forms, data entries, and biological specimens. Identifiable information, such as name, will not appear on these materials. The key linking the subject’s identity to their unique coded identifier will be kept in a confidential manner in a database on a secure server, with access only by the

principal investigator and the research staff. No names or individual identities will be used in publications resulting from the study. Physical records will be kept in an area accessible only to research staff. Research data will be stored on a secure, HIPAA-compliant server and drive with monitored and controlled access for study staff and investigators. The web-based surveys will be hosted on secure servers. In addition, participants will enter only a study ID number, thus no identifying information will be associated with their questionnaire data.

Dietary changes: Participants will be instructed to contact us if they experience discomfort, such as dehydration, constipation, diarrhea, weakness, muscle cramps, or dizziness. There is extensive instruction on how to address any potential side effects stemming from the diet. Participants will be told that their participation is voluntary and they can choose to withdraw from the study at any time without any further obligation.

Adverse events: Participants will be asked to report significant adverse events as soon as possible to study staff, and will be provided with study contact information for this purpose. The study MD will review medication use and health. We will consult with participants' primary care physicians when appropriate.

DATA AND SAFETY MONITORING PLAN

Who will perform the monitoring? The Institutional Review Board (IRB) at the University of Michigan will review all procedures and provide oversight. Internal monitoring will be done by Dr. Saslow and Dr. Kim. Additionally, we will form a Data and Safety Monitoring Board (DSMB) to monitor safety.

What will be monitored for the DSMB? The DSMB would review and comment on aspects of the trial including:

1. Study protocol
2. Participant safety: Adverse Events (AEs) and Serious Adverse Events (SAEs)
3. Participant recruitment
4. Retention rates
5. Data quality

How are adverse and serious adverse events defined?

An adverse event (AE) is generally defined as any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during the study, having been absent at baseline, or if present at baseline, appears to worsen. Adverse events are to be recorded regardless of their relationship to the study intervention. Unanticipated AEs are ones that are not previously reported or known to be associated with the study interventions. Generally, these are not mentioned in the consent form or final study protocol; however, should unanticipated adverse events, which are possibly, probably or definitely related to the intervention, become common or serious then the informed consent will be modified accordingly.

A serious adverse event (SAE) is an AE that results in one of the following:

- death – death due to any cause
- life-threatening condition – the subject was at potential risk of dying at the time of the adverse event or it is suspected that the use or continued use of the study interventions would result in the subject's death
- hospitalization – this indicates initial admission to the hospital or prolongation of a hospital stay that results from the adverse event
- disability – the adverse event has resulted in a significant, persistent, or permanent change, impairment, damage or disruptions in the subject's body function/structure, physical activities, or quality of life, and/or
- congenital anomaly – there are suspicions that exposures to the interventions prior to conception or pregnancy resulted in an adverse outcome in the child. For this study, we do not anticipate any of these based upon the inclusion/exclusion criteria of the study. If for some reason a woman was to become pregnant during the study, she would have to withdraw from the study.

What will we report to the DSMB, the NIH, and the IRB?

First, members will review the study and DSMB protocol, to assess whether it plans to report on the appropriate information for evaluating the study. Then, we will send the members reports twice a year. These reports will include safety concerns and data monitoring, including progress on recruitment, retention, and data quality. Specifically, for example, we will report on the following:

- We will describe the AEs, SAEs, participant recruitment rates, participant retention in the intervention, reasons for dropout, and participant attendance rates. We will describe whether the rates for the AEs and SAEs are consistent with pre-study assumptions.
- We will note whether the continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study and the anticipated benefit-to-risk ratio for trial participants.
- We will describe whether there are any reasons why the trial might be changed or terminated prematurely.

As considered necessary, the members will assess whether the adverse events and serious adverse events require a change, suspension, or early termination of the trial, and the members will make an independent recommendation to the study team about this. Such recommendations will be written by the board's

chairperson to the study team. This written report, in addition to a summary of the board's meeting topics, will be provided to the NIH. If any significant changes to the protocol are made, these will also be reported to the NIH. Separately, the study team will report adverse events and serious adverse events as appropriate to the University of Michigan IRB.

In the event that an SAE is identified, the board's chairperson will schedule a full meeting of the DSMB, review the results of the SAE report from the University of Michigan IRB, and determine what changes if any are necessary and if the trial should be stopped. The decisions of the IRB and the DSMB will assist the team with developing plans to implement this trial in a manner that minimizes research-related risks to participants. SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported to the DBMB, the IRBs, and NIH in accordance with requirements.

Educational training

All investigators have completed the mandatory education in Human Subjects Research. As appropriate we will also confirm that consultants and all staff working on this project have completed this training prior to working on this project. As appropriate, we will submit certificates of training at the NIH's request for "just-in-time" documents prior to potential project funding.

STATISTICAL DESIGN AND POWER

In this submission, which does not require preliminary data, we focus on pre-post analyses, which use each person as their own control. In all analyses, we will use two-tailed tests with a significance level of 0.05, and p-values will be reported. Our 4-month pilot trial retained 81% of participants. Assuming a somewhat lower retention rate of 70%, with our proposed recruitment of up to 123, the total number retained for analysis would be 84.

Aim 1: Assess acceptability and feasibility. For this aim, we will explore how measures of acceptability and feasibility change from baseline to the end of the study using a two-tailed paired *t*-test for continuous measures and a test of proportions for dichotomous measures. The magnitude and direction of the effect will be reported. Graphical summaries and Q-Q plots will assess the appropriateness of the normality assumption for the *t*-tests. If normality is not indicated, we will take remedial measures such as transformations or non-parametric analyses.

Power Aim 1: The primary outcome measure of acceptability is a 6-point Likert satisfaction score used in our pilot studies. Based on our most recent two trials of adults using our 16-week program (mean=6.0, SD=1.3; mean=6.4, SD=0.7), we conservatively used a mean of 6.0 and SD of 1.3 for our sample size calculations. Our proposed trial with approximately 84 retained participants has >90% power to detect this level of satisfaction (vs a mean of 5.0, interpreted as neutral) using a two-tailed *t*-test at an alpha level of 5%.

For the outcome of feasibility, we will record the mean number of completed sessions (out of 16 possible). We have denoted a 60% attendance of assigned sessions as our *a priori* benchmark for feasibility. Based on the completion rates from our most recent two trials of adults using our program (mean=73.9%, SD=28.9%; mean=79.3%, SD=32.4%) and using a SD of 30%, our proposed sample of up to 123 individuals has > 85% power to detect 74% completion (vs 60%) using a two-tailed *t*-test at an alpha level of 5%. We will use up to 123 participants in this analysis because attrition will be counted as less than 60% attendance.

Thus, we have at least 85% power for both primary hypotheses of Aim 1.

Aim 2: Assess changes in health and psychological outcomes. For continuous health and psychological measures, we will explore the change from baseline to the end of the study for each outcome, using a two-tailed paired *t*-test, with a significance level of 0.05. As in Aim 1, we will test the assumption of normality and remediate as necessary. For the dichotomous variable measuring achievement of glycemic control, we will report descriptive statistics in comparison to other interventions, such as the Diabetes Prevention Program.⁹⁶

Power Aim 2: To estimate the number of subjects needed for the outcome of HbA1c, we note that the DPP showed a 0.1% decrease in HbA1c with a standard deviation of the difference approximately equal to 0.1%.⁹⁷ This decrease in HbA1c was deemed clinically significant because it led to a clear reduction in type 2 diabetes incidence compared to control. The DPP's standard deviation estimate of 0.1% is consistent with two studies of very low-carbohydrate diets in adults with prediabetes.^{98,99} Thus, we used 0.1% as the standard deviation in our sample size calculation. For a two-sided, paired *t*-test to detect a clinically meaningful difference of 0.1% and a standard deviation of 0.1%, we have over 90% power with 84 retained participants.

For the outcome of weight, our sample size calculation was computed based on the smallest effect size among several measures of weight loss that we observed in the pilot. The smallest effect size observed in our pilot data was 0.54, for a threshold of 5% weight loss. Thus, in our sample size calculations, we used Cohen's "moderate" effect size of 0.5 as the minimum effect size for main effects of all factors. In absolute terms, our pilot results showed 4.6 kg greater weight loss than the controls, which is greater than the difference observed in the DPP (a 3.5 kg difference) which was associated with a 39% reduction in the onset of type 2 diabetes in overweight and obese adults. To detect a moderate effect size of 0.5, as observed in our pilot, would require a sample of size 34. Our sample of 84 retained participant will be adequate.

Aim 3: Assess factors that identify individuals who will particularly benefit from the intervention.

These moderation analyses will contribute to a nascent research approach for personalized nutrition, which responds to Objective 2-5 of the NIH's May 2020 Strategic Plan for NIH Nutrition Research. To characterize

the heterogeneity of intervention effects among participants for change in HbA1c, we will regress change in the outcome as a function of moderating variables of sex, literacy, emotional eating, and glycemic control. A statistically significant moderator would indicate the need for further investigation of that variable's role. Distributional assumptions will be evaluated and remediated as necessary. For example, we will examine residual plots and examine goodness of fit using standard techniques. This analysis will be largely exploratory to generate effect size estimates and to design a future randomized controlled trial.

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