Title: Towards understanding the relationship between meals and blood biomarkers

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Significance
The long-term objective of this project is to create a counterfactual-based lifestyle intervention that curtails the progression of prediabetes to T2DM through management and knowledge of food choices. This is a significant objective since 70% of prediabetes patients go on to develop T2DM. The project addresses a major objective of PATHS-UP in general and Thrust 4 in particular, by developing an innovative behavior-change intervention that will eventually make use of information from the Lab-on-your-Wrist device.

Innovation
To our knowledge, this is the first project to (1) propose an intervention based on counterfactual thinking for diabetes prevention and (2) combine continuous glucose monitors (CGMs) and food photography to promote a better understanding of how food choices affect blood glucose.

Specific Aim
The specific aim of this project is to establish the validity of leveraging photo-based food diaries and CGMs to engage counterfactual thinking strategies that improve food choices amongst prediabetes participants. This will be measured by changes in (1) eating attitudes and behaviors, (2) behavioral intentions to improve healthy eating behavior, (3) motivation to improve eating behavior, (4) increased self- efficacy for healthy eating, and (5) number of glucose excursions and time-in-range.

Approach
Study design: We will recruit up to 40 subjects diagnosed with Type 2 diabetes and prescribe glucose-lowering medication(s). Informed consent will be obtained on the screening day before any study related procedures will be performed. Blood will be sampled through venipuncutre technique on the upper arm. A blood sample of 4 mL will be collected for each measurement of the subject's A1c. A total of 8 mL will be collected for the whole study, one on the screening visit and one on the last study day. If inclusion/exclusion criteria are met, subjects are invited to take part in the study. The study involves 1 screening visit lasting up to 2 hours and fasting prior to screening is required. We will screen the subjects for any disease or condition that could interfere with the studies and complete study related questionnaires.

On the first study day, we will place the Freestyle Libre Pro and continue monitoring for 2 weeks. Subjects will also complete baseline behavioral measures/dietary habit questionnaires. During this time, participants will be asked to take at least 3 photographs of their meals and send them to the researchers via text-messaging using MyCAP. Communication with participants via MyCAP will be done to confirm receipt of photos (e.g., “Good job with the photos yesterday, keep it up today!”), reminders if photos are missed (e.g., “It seems you sent fewer photos yesterday than your survey indicates meals you eat. If you missed a picture yesterday, remember to try and take photographs of all food today.”), or tips to improve photos for image analysis (e.g., “Good job with the photos yesterday, but please try to adjust lighting/focus to properly capture all food.”).

The subject will return after continuous wearing of the CGM monitor and sending of photos after the 2 weeks. At this second study day the CGM will be replaced and all data on the old CGM will be downloaded by the

researchers. The subject will then wear the new CGM monitor and continue to send pictures of all meals for 1 week before returning for their third visit.

At the third visit, a new CGM will be placed and the subject will be randomized into behavioral intervention.

1. One intervention will be based on counterfactual thinking, which will allow the subjects to think of an alternative reality that “might have been” based on the concurrency of their glucose readings and the meals they ate.
2. The control condition will use reflective writing. These subjects will be engaged in reflective writing intervention. They will look at your CGM readings throughout the first two weeks and compare them to the food eaten at those specific times. They will then be asked to reflect on the meals and how they feel about the changes in glucose levels based on the food choices made.

After this visit, they will then continue to wear the CGM monitor and take photos of their meals. They will return for their fourth visit in 2 weeks.

The fourth visit will consist of permanently removing the CGM monitor and conducting post-treatment interviews and behavioral measures/dietary habits with the subjects.

Subjects will return for their fifth and sixth follow-up visit 2 months post intervention. At each of these visits their A1c will be measured through a blood collection of 4 mL by venipuncture. Delayed post-test interviews, and behavioral measures/dietary habits will also be conducted.

<u>Description of the CBLI intervention</u>

In the CBLI, participants will be shown healthy (low PPGR) and unhealthy (high PPGR) samples of their food photographs with the corresponding glucose responses (see Data Synchronization & Meal Selection & Figure 1b). For counterfactuals to be an effective self-regulatory tool, one needs information from a personal negative experience relevant to the current goal. Using healthy and unhealthy meal selections and their resulting CGM responses will make the causal relationship between food choices and glucose response more salient, and will increase the effectiveness of the counterfactual intervention, in which they generate ways they could have changed their food choices and subsequently improved the CGM response. Participants will be asked to compare the healthy and unhealthy meals and generate counterfactuals about how they could have altered the unhealthy meal (e.g., replace white bread with a tortilla) such that it would have improved the outcome (i.e., lower glucose responses). To increase the likelihood of participants generating accurate counterfactuals that could have improved their PPGR outcome, participants will be provided lists of effective eating strategies to aid their counterfactual generation. Afterwards, participants will evaluate each counterfactual thought and list at least one situation in the near future in which they could implement the eating behavior described in the counterfactual, and describe any barriers they imagine could reduce the likelihood of implementing the behavior. Our expectation is that the counterfactual thoughts generated during the intervention will lead to better food choices and increased motivation in the weeks that follow.

This session will be video recorded to ensure treatment fidelity and code participant responses.

<u>Behavioral measures/dietary habit Questionnaires</u>

General Health Intentions. Designed to collect ratings of intentions to engage in healthier food habits over the next six months.

Motivation. The Regulation of Eating Behaviors Scale is designed to measure subject motivations for eating including to cope with negative affect, to be social, to comply with others’ expectations, and to enhance pleasure.

Self-efficacy & Self-Regulation. Measured by the 5-item Eating Self-efficacy Scale and the Self-regulation of Eating Behavior Questionnaire.
Behavioral Intentions. Three items designed based on the Theory of Planned Behavior to measure intention to eat healthy using counterfactual strategies developed in Study Visit #3 (intervention group only).

Inclusion criteria

- Ability to walk, sit down and stand up independently
- Diagnosed with type 2 diabetes (T2D) and take glucose-lowering medication(s).
- Motivated to learn how to regulate blood glucose through non-medical intervention such as changes to eating behavior
- Subject is judged to be in satisfactory health based on medical history, physical examination
- Willingness and ability to comply with the protocol
    - Use your smartphone to upload pictures of meals through MyCap

Exclusion criteria

- Subject has planned elective surgery requiring 2 or more days of hospitalization during the entire study
- Allergy to adhesives
- Planned medical procedures that are documented to interfere with CGM readings, such as
    - Xylose absorption testing (oral sugar testing)
    - CT
    - MRI
    - X-ray
    - Diathermy treatment (high-frequency electric current to stimulate heat generation within body tissues)
- Established diagnosis of malignancy
- Presence of acute illness or metabolically unstable chronic illness
- Any other condition according to the PI, nurse, or study coordinator that was found during the screening visit, that would interfere with the study or safety of the patient
- Failure to give informed consent or Investigator's uncertainty about the willingness or ability of the subject to comply with the protocol requirements

When during the period from enrollment to completion of the study any condition is developed, whether causing the subject to not meet inclusion criteria or to meet exclusion criteria, the subject will be excluded from the study. Family history of type 2 diabetes will be used only for post-stratification of those who can report.